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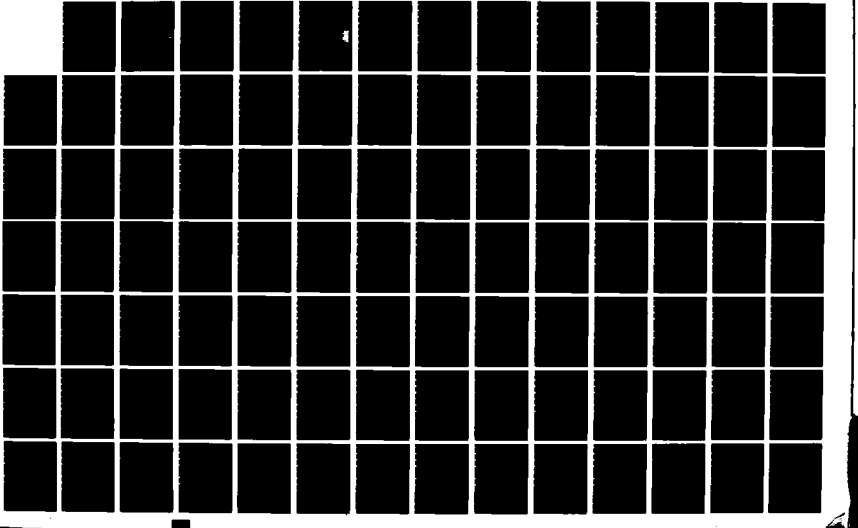

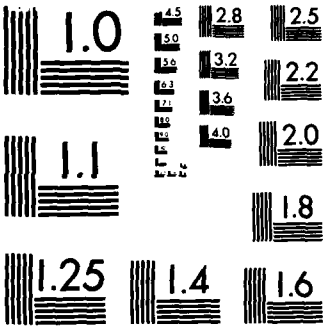

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I. INTRODUCTION

A. Mapping of forebrain dopamine systems

The existence of dopamine in the brain was first reported over 25 years ago (Carlsson et al. 1958), and subsequent fluorescent histochemical techniques provided strong evidence of monoaminergic pathways from the midbrain to the forebrain (Anden et al. 1964). The identification of dopamine as one of the monoaminergic transmitters in this pathway sparked considerable behavioral and neurochemical research on the basal ganglia (Anden et al. 1966a). Two major dopamine pathways have been identified, the nigrostriatal pathway arising from the substantia nigra pars compacta coursing to the striatum, and the mesolimbic pathway arising from cell bodies near the interpeduncular nucleus (medial to the substantia nigra) which innervates the nucleus accumbens (NAS), the olfactory tubercle, and the frontal cortex (Lindvall and Bjorklund 1974). The vast majority of brain dopamine is contained within these two systems (Horn et al. 1974; Versteeg et al. 1976; Palkovits 1979). Other dopamine-containing pathways include the tubero-infundibular pathway, the incerto-hypothalamic pathway and the periventricular system (Lindvall and Bjorklund 1974; Lindvall 1979).

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MESOLIMBIC AND NIGROSTRIATAL DOPAMINERGIC SYSTEMS: BEHAVIORAL NEUROPHARMACOLOGY

by

Stanley Lynn Hartgraves

A Dissertation Presented to the

FACULTY OF THE GRADUATE SCHOOL

UNIVERSITY OF SOUTHERN CALIFORNIA

In Partial Fulfillment of the

Requirements for the Degree

DOCTOR OF PHILOSOPHY

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This dissertation, written by

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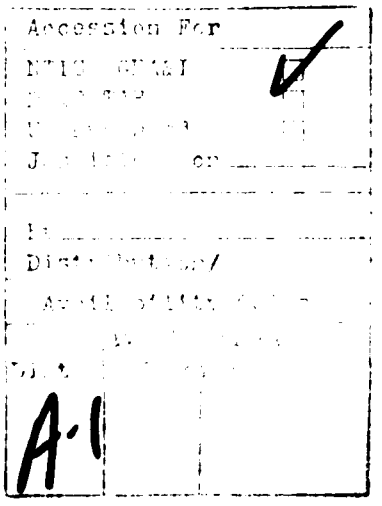
My family, especially my wife Edna, deserve great credit for their support and help. My Mother and Father provided much needed, long-distance encouragement and support.



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The mesolimbic dopamine system receives input from limbic-associated structures such as the amygdala, hippocampus, frontal cortex and cingulate gyrus (Haber et al. 1982; Haber and Watson 1985), thus suggesting the importance of this system as an interface between the limbic and motor systems (Mogenson et al. 1980). In contrast, the striatum, especially the dorsolateral portion, receives predominantly sensory-motor related afferents (Kelley et al. 1982; Haber et al. 1982).

The efferent pathways of the two major dopamine systems have been studied extensively by neuroscientists in the last decade, and the concept of a single dominant pathway (or classical output pathway) for the basal ganglia has been greatly modified. The classical output pathway consists of fibers arising from the striatum travelling to the external and internal segments of the globus pallidus (the entopeduncular nucleus of the rat is similar to the internal segment of the globus pallidus in primates and humans), and thence to the ventral nuclei of the thalamus (Papez 1942; Szabo 1962; Nauta and Mehler 1966; Carpenter 1983). The thalamus in turn projects to motor and premotor cortex (Walker 1938; Strick 1971), which represents a major motor output (Carman et al. 1963; Carman et al. 1965; Kemp and Powell 1970; McGeer et al. 1977). The other, more recently proposed output pathway of the basal ganglia is composed of fibers originating in the forebrain (especially the striatum) which synapse in the

substantia nigra pars reticulata (Garcia-Munoz et al. 1977; Marshall et al. 1977a; DiChiara et al. 1978; James and Starr 1978; Olianas et al 1978; Dray and Oakley 1978). This pathway was originally believed to subserve feedback regulation of substantia nigra dopaminergic neurons (Anden and Stock 1973; Bunney and Aghajanian 1976), but now has been shown to mediate most striatal associated functions. The fiber pathways from the substantia nigra pars reticulata project to the ventral nuclei of the thalamus, the superior colliculus and the reticular formation (Rinvik 1975; Carpenter et al. 1976; Clavier et al. 1976; Vincent et al. 1978; DiChiara et al. 1979a). This output pathway has a more direct influence on motor structures in lower brain regions, underlining its importance.

Despite the different areas involved in the two output pathways, there are striking similarities between the medial pallidal segment and the substantia nigra pars reticulata as reported by Carpenter (1981), " (1) cells and synaptic terminals bear strong morphological resemblances; (2) both receive major afferents from the striatum that have similar neurotransmitters; (3) both receive inputs from the subthalamic nucleus; (4) neither receives inputs from the cerebral cortex or thalamus; (5) both have major thalamic projections to distinctive ventral tier thalamic nuclei without overlap."

B. Dopamine receptor subtypes

The behavioral consequences of stimulating the above dopamine containing systems has been ascribed to drug interactions with dopamine receptor complexes. Thus, as in other neurotransmitter systems such as acetylcholine (nicotinic and muscarinic receptors), noradrenaline (alpha and beta receptors), histamine (H-1 and H-2 receptors) and serotonin (S-1 and S-2 receptors), dopamine is also thought to interact with two basic receptors, termed the D-1 and D-2 receptors (Kebabian and Calne 1979). The D-1 receptor is linked to the stimulation of adenylate cyclase, while the D-2 receptor is apparently unlinked or negatively linked to adenylate cyclase (Kebabian and Calne 1979; Stoof and Kebabian 1981; Onali et al. 1984). Early work on the dopamine receptor was directed toward dopamine stimulation of adenylate cyclase (Kebabian et al. 1972; Iversen 1975), prompting the idea that dopamine-sensitive adenylate cyclase might be the dopamine receptor (Kebabian et al. 1972). However, through further pharmacological studies of the rat striatum, the existence of the D-2 receptor was also confirmed (Creese et al. 1977; Sibley and Creese 1980; Stefanini et al. 1980).

Pharmacological studies have become more effective in differentiating between D-1 and D-2 receptors, especially in the last 2-3 years. Whereas bromocriptine and other ergots as well as

affinity agonists at the D-2 receptor (Kebabian and Calne 1979; Gundlach et al. 1983), butyrophenones such as haloperidol (Beart 1982; Creese et al. 1983) and the atypical neuroleptic sulpiride (Munemura et al. 1980) are effective antagonists . The D-1 receptor appears to be stimulated preferentially by SKF 38393 (Setler et al. 1978) and antagonized by SCH 23390 (Hyttel 1983). Interestingly, even though the D-1 receptor was the first to be discovered and presumably all actions of dopaminergic drugs tied to its stimulation, the discovery of the D-2 receptor led to the reverse suggestion, i.e. most behavioral actions of agonists and antagonists are due to D-2 binding (Seeman 1980; Joyce 1984). In fact, many authors, even as recently as 1984 report no apparent physiological role for the D-1 receptor (Creese 1982; Woodruff et al. 1984). It now logically appears that both receptors are involved in dopamine receptor-stimulated behaviors. Thus, either D-1 or D-2 receptor blockade causes catalepsy (Christensen et al. 1984), although D-1 antagonist-induced catalepsy is not reversed by anticholinergics (Hyttel and Christensen 1983), while D-2 antagonist-induced catalepsy is (Costall and Naylor 1974; Ezrin-Waters et al. 1976). The fact that D-2 receptors have been associated with striatal cholinergic interneurons both pharmacologically (Sethy 79; Scatton 82) and anatomically (Joyce and Marshall 1985) suggests the striatum as the site for the reversal of D-2 mediated catalepsy; However, cholinergic-induced

catalepsy and anticholinergic reversal of neuroleptic-induced catalepsy does not occur in the striatum (Costall and Olley 1971; Costall et al. 1972; Costall and Naylor 1973). Research in this lab also suggests that behaviors such as biting and licking (typically caused by high doses of apomorphine) seem to be preferentially linked to the D-1 receptor. In this paradigm, pretreatment of mice with low doses of sulpiride enhanced the ability of apomorphine to cause biting and licking (Yurek and Randall 1985). Other studies also suggest a link between D-1 receptors and oral behaviors (Rosengarten et al. 1983). The opposite effects of D-1 or D-2 receptor stimulation on substance P like activity in the substantia nigra further suggest functional roles for both receptors (Oblin et al. 1984; Sonsalla et al. 1984).

The anatomical localization of the two dopamine receptor subtypes may indicate additional functional differences. D-2 receptors are located on striatal afferents from the cortex (Garau et al. 1978; Schwarcz et al. 1978), as autoreceptors on nigral neuronal cell bodies projecting to the striatum and on the nerve terminals of these neurons (Aghajanian and Bunney 1973; Sokoloff et al. 1980), and on neurons in the striatum (Sokoloff et al. 1980; Severson and Randall 1983). D-1 receptors have been associated with striatal neurons (Cross and Waddington 1981; Leff et al. 1981) and nerve terminals of striato-nigral neurons in the substantia nigra pars reticulata (Cross and Owen 1980).

C. Dopamine receptor supersensitization

Dopamine receptor up-regulation or supersensitization was first suggested by Ungerstedt (1971ab) to explain enhanced behavioral responses to dopamine agonists following dopamine depletion of the forebrain with the selective neurotoxin 6-hydroxydopamine (6-OHDA). The process that occurred in the brain was felt to result from mechanisms similar to those occurring in the periphery following denervation of muscle fibers. Later studies also confirmed that hypersensitive responses to dopamine agonists could result from sustained dopamine synthesis inhibition or depletion of dopamine stores (Tarsy and Baldessarini 1974) and by chronic dopamine receptor blockade (Gianutsos et al. 1974; Eibergen and Carlsson 1976). However, it was not until 1977 when Burt et al. and Creese et al. demonstrated that chronic dopamine receptor blockade or 6-OHDA-induced lesion resulted in quantifiable increases in dopamine receptor number (approximately 30%) as defined by ^{3}H-neuroleptic binding. Up-regulation of D-1 receptors is less clear. It now appears that a major task confronting behavioral neuropharmacologists is to account for shifts in the dose-response curve for dopamine agonist-induced behaviors of up to 100 fold (Marshall and Ungerstedt 1977; Ungerstedt et al. 1978) supposedly caused by the modest 6-OHDA-induced increase in dopamine receptor number.

D. Dissertation goals

The main thrust of these studies is to selectively examine drug-induced behaviors of each of the two major dopamine systems by the use of 6-hydroxydopamine. With receptor up-regulation enhancing the response of the targeted structure, motor functions of each will be tested against various dopamine agonists. Drug-induced motor behaviors that will be examined include locomotor activity (section III), stereotypy (section IV) and circling (section V). Section V is an especially important section, since interactions between the nucleus accumbens and the striatum will be examined for each of the aforementioned behaviors. The remainder of this introduction will include brief descriptions of two human disorders that involve the dopamine systems.

E. Disorders associated with malfunctioning dopamine systems

Parkinson's Disease

Parkinson's disease is the most familiar disease associated with a malfunctioning dopamine system. The degeneration of nigrostriatal neurons in this disease, first described by Ehringer and Hornykiewicz (1960), is well known and has been confirmed

numerous times. More recent studies from Hornykiewicz's laboratory, however, show that dopamine neuron degeneration is not restricted to the nigrostriatal system. Thus, in Parkinson's disease decreases of dopamine concentration in the nucleus accumbens are as severe as those in the striatum (Farley et al. 1977; Price et al. 1978). In confirmation of these studies, dopamine and tyrosine hydroxylase, the rate-limiting enzyme in catecholamine synthesis, are decreased in the brains of Parkinsonian patients, both in the substantia nigra and in the ventral tegmental area which contain the cell bodies of mesolimbic and mesocortical dopamine neurons (Javoy-Agid et al. 1981ab). Thus, studies which examine the effects of drugs on both the mesolimbic and nigrostriatal system will provide a clearer picture of the functioning of each system and give insights into how the systems interact.

Schizophrenia

Another disease state proposed to affect the dopamine system is the affective disease schizophrenia. There are theories that this disease state may represent an overactive mesolimbic/mesocortical dopamine system (Snyder 1972; Stevens 1973; Thierry et al. 1973; Hokfelt et al. 1974). Thus, drugs which lead to improvement in affective symptoms (via blockade of receptors in the mesolimbic/mesocortical dopamine system) can

ultimately cause orofacial dyskinesias (symptoms associated with chronic striatal dopamine receptor blockade). One of the potential benefits of research involving dopaminergic drug actions in the basal ganglia, is the possibility of finding a drug or drug combination with preferential antipsychotic activity with no motoric side effects.

II. GENERAL MATERIALS AND METHODS

A. Surgical Procedures

Adult male Sprague-Dawley rats weighing 300 + 50g were anesthetized with Equithesin (3.5 ml/kg) and positioned in a stereotaxic apparatus (Kopf). Coordinates for the various procedures are presented below in Table I (Pellegrino and Cushman 1967).

TABLE I
Coordinates for stereotaxic placements

Region	Ant(+)/Post(-)	Lat	Vent
	Injection tips		
NAS	3.4	1.7	7.2
STR	2.0	3.0	5.0
	6OHDA infusions		
NAS	3.4	1.7	7.2
SNC-STR	0.8	3.5	6.0
MFB	-0.5	1.8	8.7
	Electrolytic lesions		
STR-SNR	-1.5	3.6	7.2

Millimeters anterior and posterior to bregma. Guide cannulae (through which injection tips protruded) were implanted 2 mm above the desired region. Nucleus accumbens (NAS), striatum (STR), substantia nigra pars compacta to striatum dopamine pathway (SNC-STR), medial forebrain bundle (MFB), striatum to substantia

nigra pars reticulata pathway (STR-SNR).

6-OHDA hydrobromide (8 ug, expressed as base, Sigma) was dissolved in saline containing 0.2 mg/ml ascorbic acid and infused in a volume of 2 ul at a rate of 1 ul/min. The injection cannula was left in place an additional minute following the end of the infusion. Infusions of 6-OHDA, intended to deplete striatal dopamine with minimal NAS depletion, were made in the tail of the caudate (Jackson et al. 1983). NAS 6-OHDA infusions were made directly into the center of the nucleus. Electrolytic lesions (2mA for 20 seconds) were made with a Grass model DCLM5A lesion maker and a 0.02 mm diameter platinum-iridium electrode which was insulated except for 0.2-0.5 mm at the tip with teflon and an additional layer of Stoner-Mudge coating. A rectal probe coated with petroleum jelly completed the circuit.

B. Intracerebral and Systemic Injections

Intracerebral infusions were made in unanesthetized, manually restrained rats. The injections were made through 30-guage stainless steel cannulae attached by polyethylene tubing to motor-driven microsyringes. The tips of the injection cannulae protruded 2 mm beyond the tips of the guide cannulae, so as to terminate in the desired region. The infusions were monitored by watching the progress of a small air bubble introduced into the

polyethylene tubing. Striatal infusions were typically in a volume of 1.0 ul (0.22 ul/min), except for SKF 38393 (2.0-3.0 ul) and where much higher doses of drugs were used to elicit rotation. NAS infusion volume was 0.5 ul at a rate of 0.11 ul/min. The volume and rate of infusion into the NAS was decided upon following infusion of (3H)Muscimol at two different volumes and rates of infusion (Table II). As can be seen in Table II, compared to the 1 ul injection, the amount of radioactivity in the nucleus accumbens was reduced by only 32%, whereas the corresponding decreases for frontal cortex, caudate nucleus and rest of brain were 74%, 67% and 48%. Thus, lower infusion volume and a slower rate of infusion into the NAS resulted in better localization of injected material.

TABLE II

Regional distribution of radioactivity 1 hour after injection

Region	Total cpm 1ul inj.	Total cpm 0.5ul inj.
OT	3,887 ± 1,087	4,216 ± 1076
NAS	32,979 ± 5,741	22,413 ± 1,471
FCX	24,633 ± 5,399	6,423 ± 2,363
STR	12,853 ± 2,169	4,303 ± 753
Rest	24,760 ± 6,318	12,878 ± 2,292

Mean ± SEM of 6 rats (1ul injection) and 7 rats (0.5ul injection). The (^{3}H)muscimol solution was 80 ng/ul and 200,492 cpm/ul (counts per minute/microliter). Injections (inj.) were bilateral, and left and right brain regions were pooled. The 1ul injection was at the rate of 1 ul/min and the injector left in place an additional minute. The 0.5 ul injection was at the rate of 0.11 ul/min and the injector left in place an additional 2.5 min. Olfactory tubercle (OT), Nucleus Accumbens (NAS), Frontal

cortex (FCX), Striatum (STR), Rest of brain (Rest).

Systemic injections were made subcutaneously (sc) behind the neck, in a volume of 1.0 ml/kg. A list of the drugs used in this study and the vehicle used to dissolve each is presented in Table III.

Table III
List of drugs

Drug	Vehicle
Intracerebral infusions	
Dopamine agonists	
Apomorphine hydrochloride	0.1% Na metabisulfite
LY 151777	0.9% saline
SKF 38393	water
Dopamine antagonists	
Haloperidol	1.0% lactic acid
Sulpiride	1.0% lactic acid
GABA-ergic agents	
Muscimol	0.9% saline
GABA	0.9% saline
Picrotoxin	0.9%saline
Systemic injections	
Dopamine agents	
d-Amphetamine sulfate	0.9% saline
Apomorphine hydrochloride	0.9% saline
L-Dopa/carbidopa	warmed saline,HCL,pH to 6.0
Lergotrile	water
N-n-propylnorapomorphine	0.9% saline
Lisuride	0.9% saline
Pergolide	0.9% saline
Piribedil	water,HCL,pH to 7.2
Bromocriptine	tartaric acid,ethanol,sal.
Haloperidol	1.0% lactic acid

C. Behavioral Measurements

It should be emphasized in this section that all behavioral studies that utilized mechanical means of measurement were also subject to direct observation to verify recorded behavior.

Stereotypic behavior was directly observed in 30cm x 30cm x 30cm square 1.25 cm wire mesh cages. Animals engaged in stereotypic grooming were timed with stop watches, with mouth contact of body surfaces required to start the watches. Testing was discontinued and rats administered anesthetics if they began to excessively damage their forepaws.

Locomotor hyperactivity was measured in banks of wire activity cages (40cm x 24cm x 18cm). The cages were equipped with a single light-emitting diode, situated 2.4 cm above the floor of the cage and aimed at a photodetector on the opposite side, so that the infrared beam crossed the long axis of the cage. Beam interruptions per 10 minute period were automatically recorded and printed by a modified (G and B Electronics, Royston, U.K.) AIM 65 (Rockwell) microcomputer. Animals were habituated for 30 minutes prior to injections.

Drug-induced rotation was measured by both trained observer and by video-tape recording. In studies using an observer, rats were placed in transparent hemispherical plastic bowls (diameter 36 cm) and the number of 360 degree turns per minute was recorded

every 10 minutes. Time-lapse video-tape recording (7:1 time ratio) was made using a Sanyo VC-1200 recorder. The camera was mounted above the hemispherical bowls, allowing simultaneous recording of up to 12 rats. Rotational behavior was then scored from the recording by typing data into an Apple II computer equipped with a John Bell Engineering, Inc. 6522 Parallel I/O card (n79-295, San Carlos, Ca.) for timing purposes.

D. Biochemical Measurements

After completion of studies, rats were killed by decapitation, and their brains rapidly removed and placed on ice cold glass plates. The striata, NAS and olfactory tubercles were then dissected (Glowinski and Iversen 1966; Horn et al. 1974). The radioenzymatic assay for dopamine was slightly modified from existing methods (Moore and Phillipson 1975; Umezu and Moore 1979; Osterburg et al. 1981). Brain tissue was weighed and homogenized in 50 volumes of 0.1N HCL containing 5 mM EGTA and 5 mM glutathione. The acidified homogenates were centrifuged at 10,000 g (x force of gravity) for 1 minute in a microfuge. 10 ul aliquots of the supernatants were added to 12 ml conical centrifuge tubes on ice. To each tube were then added 26 ul of "incubation mixture". This mixture (for 30 assays) contained 49 ul of dithiothreitol (0.2 M in 0.2 M magnesium chloride), 27 ul of S-adenosyl-L-(methyl-3H)methionine (15 Ci/mmole, 1mCi/ml,

Amersham), 122 ul of freshly prepared pargyline hydrochloride (10.2 mM), 326 ul of 1 M Tris pH 10.8, 246 ul of 0.1 M sodium phosphate buffer containing 10 mM EGTA, pH 7.0, and 90 ul of catechol-O-methyltransferase prepared as described previously (Moore and Phillipson 1975). The mixture was incubated at 37 degrees centigrade for 45 minutes. Thirty ul of 0.5 M sodium borate buffer, pH 11, were then added, followed by 2 ml of toluene/isoamyl alcohol (3:2). Tubes were vortexed for 30 seconds, centrifuged (1000 g, 5 min), and 1.8 mls of the upper layer pipetted into tubes containing 100 ul of 0.1 M acetic acid plus 25 ug each of normetanephrine and 3-methoxytyramine. These tubes were vortexed (30 seconds), centrifuged (1000 g, 5 min) and the upper layer removed by aspiration. The acid phase was washed with 2 ml of toluene/isoamyl alcohol (3:2). Plastic TLC sheets precoated with silica gel and containing a fluorescent marker were spotted first with 5 ul of methoxyamine carrier solution (10 mg/ml each of normetanephrine and 3-methoxytyramine in 0.1% sodium metabisulfite) and then with 2X 10 ul portions of the acid phase. Chromatographs were developed ascending in freshly prepared methylamine:ethanol:chloroform (5:18:40), air dried, and spots visualized under ultraviolet light. The 3-methoxytyramine spots were cut out, placed in scintillation vials, and eluted by shaking for 45 minutes with 1 ml of freshly prepared ethyl acetate/glacial acetic acid/water (3:3:1). 10 ml of scintillant (0.5 % PPO in toluene/ethanol, 7:3) were added to each vial and radioactivity

determined by liquid scintillation counting. External standards (0.25, 0.5, 1.0 and 2.0 ng of dopamine) dissolved in 0.1 N HCL/5 mM EGTA/5 mM glutathione and blanks, consisting of this solution alone, were included in each assay. Radioactivity above blank increased linearly with amount of dopamine.

Biochemical measures of dopamine depletion and ^{3}H-spiperone binding in the striatonigral output model of circling behavior were done in other laboratories. Specific ^{3}H-spiperone binding was measured by filtration assay (Burt et al. 1976) as modified by Severson and Finch (1980). This work was done in Dr. James A. Severson's lab at the University of Southern California Medical School. High performance liquid chromatography was performed at Dr. Richard Wilcox's lab at the University of Texas.

E. Histology

After the termination of behavioral experiments, rats (whose brain tissues were not used for assay of dopamine) were deeply anesthetized with Equithesin and perfused intracardially with 10% formalin. Brains were left in 30% sucrose for at least 2 days until they sank. Frozen sections (48 um) were then cut in a cryostat, mounted and stained with either thionin or cresyl violet, to verify infusion sites as well as electrolytic lesion sites.

F. Statistical methods

ANOVA (analysis of variance), paired and pooled, 2-tailed t-tests and Mann-Whitney U tests were used to analyze data, with the 0.05 level of confidence required for significance.

III. MESOLIMBIC SYSTEM

A. Introduction

Locomotor hyperactivity elicited by amphetamine was thought to involve the dopaminergic systems, but not until the pioneering work of Kelly et al. (1975) and Pijnenburg et al. (1973, 1975) was the association of the NAS with this behavior confirmed. Infusions of dopamine, d-amphetamine, ergometrine (Pijnenburg and Van Rossum 1973; Pijnenburg et al. 1973; Pijnenburg et al. 1976) and 2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (Elkhawad and Woodruff 1975) directly into the NAS resulted in locomotor hyperactivity . 6-OHDA-induced lesions of the NAS blocked locomotor hyperactivity, while lesions of the striatum enhanced the locomotor stimulant actions of amphetamine (Kelly et al. 1975).

Other neurotransmitters are found in the NAS and influence locomotor hyperactivity. Gamma-aminobutyric acid (GABA) and its synthesizing enzyme glutamic acid decarboxylase are found in the NAS (Balcom et al. 1975; Lloyd et al. 1977; Fonnum et al. 1977; McGeer et al. 1978), with GABA apparently antagonizing dopamine-mediated locomotor hyperactivity. Thus, GABA infused

into the NAS attenuated dopamine-stimulated locomotor activity (Jones et al. 1981), and intraaccumbens muscimol (a potent GABA agonist) blocked intraaccumbens ergometrine-induced locomotor activity (Scheel-Kruger et al. 1977a), as well as systemic apomorphine-induced motility (Scheel-Kruger et al. 1977b). The NAS also contains acetylcholine (ACh) and its synthesizing enzyme choline acetyltransferase (Shute and Lewis 1967; Heimer and Wilson 1975; Jacobowitz and Goldberg 1977; Walaas and Fonnum 1979), however, the behavioral effects of intra-NAS ACh are unclear. Low doses of carbamyl chloride infused with dopamine into the NAS potentiated locomotor hyperactivity, while higher doses produced no significant effect (Jones et al. 1981). Others report that intra-NAS infusions of physostigmine and arecoline supress intra-NAS dopamine-induced locomotor activity (Costall et al. 1979). 5-hydroxytryptamine (5HT) fibers from the raphe nucleus also influence the NAS (Conrad et al. 1974; Geyer et al. 1976), with the predominant effect of intra-NAS 5HT being a reduction of intra-NAS dopamine-stimulated locomotor activity (Costall et al. 1976a; Jones et al. 1981). Amphetamine-induced locomotor activity is also antagonized by infusion of 5HT into the NAS (Carter and Pycock 1978). Other proposed transmitters having effects on NAS mediated locomotor activity include neuropeptides. Thus, bombesin (a tetradecapeptide) induces locomotor hyperactivity when infused into the NAS (Schulz et al. 1984); neurotensin (a tridecapeptide) infused into the NAS blocks prior dopamine-induced locomotor

activity (Kalivas et al. 1984); and, sulfated cholecystokinin octapeptide intra-NAS blocks intra-NAS apomorphine-induced locomotor hyperactivity (Vaccarino and Koob 1984).

In this section, I will examine the effects of a series of dopaminergic agonists in animals with bilateral 6-OHDA-induced lesions of the NAS. This will be contrasted with the effects of apomorphine-induced locomotor hyperactivity in control animals.

B. Experimental design

To derive dose response curves for apomorphine-induced locomotor hyperactivity in controls (n=12), a 6 x 6, 2 replicates, balanced Latin square was used, with 3-4 days between testing. For dopaminergic agonist-induced locomotor hyperactivity in animals with supersensitive NAS (n=8 each drug), balanced Latin squares (4 x 4, 2 replicates) were used. In intracerebral infusion experiments, animals were tested using a cross-over format. Experiments were run a minimum of two weeks following lesions with 6-OHDA to allow for supersensitization, and at least one week following cannulation only.

C. Results

Systemic injections of apomorphine in animals with intact NAS

Figure 1 shows light beam interruptions at each dose for each 10 minute period. Only the dose of 0.2 mg/kg caused significant increases in locomotion in the absence of stereotypic activity. Doses of 0.4 mg/kg and higher caused stereotypic activity during the time when brain drug concentrations were high, which switched to locomotor hyperactivity when the high dose effect began to wane. At 3.2 mg/kg the animals engaged in stereotypic activity throughout the 1 hour session, with little locomotor activity observed.

Systemic injections of dopamine agonists and saline in animals with bilateral 6-OHDA-induced lesions of NAS

Figure 2 depicts the light beam interruptions per 10 minute period for 4 doses of apomorphine. In figures 3-8, the total light beam interruptions during the test period for the remaining dopaminergic drugs are presented. The time periods chosen for each drug usually represent the time necessary for the drug effects to subside close to control values. Two exceptions are the high dose of lergotrile (5.0 mg/kg) and the two highest doses of pergolide (0.4 and 0.2 mg/kg). In both of these cases, the effects of the agonists were close to their peak effects even after 9 hours.

Figure 1. Dose-response data for apomorphine-induced locomotor activity in control animals. Each dose is represented in each time period (left to right: 0.1 mg/kg, 0.2, 0.4, 0.8, 1.6 and 3.2 mg/kg). Vehicle injected control data precedes the intial dose in each period. Solid line near bottom of figure represents last 10 minutes of habituation (12 $\pm$ 2 locomotor counts). There was an overall significant effect of treatment ($F(5,216) = 9.01$; $p < 0.01$), overall time effect ($F(5,216) = 3.45$; $p < 0.01$) and dose by time interaction ($F(30,216) = 5.97$; $p < 0.01$). There was a significant effect of treatment during the 30 - 60 minute time periods only ($F(5,216) = 8.62$ at 30', $= 8.90$ at 40', $= 11.04$ at 50' and $= 13.88$ at 60'; $p < 0.01$).

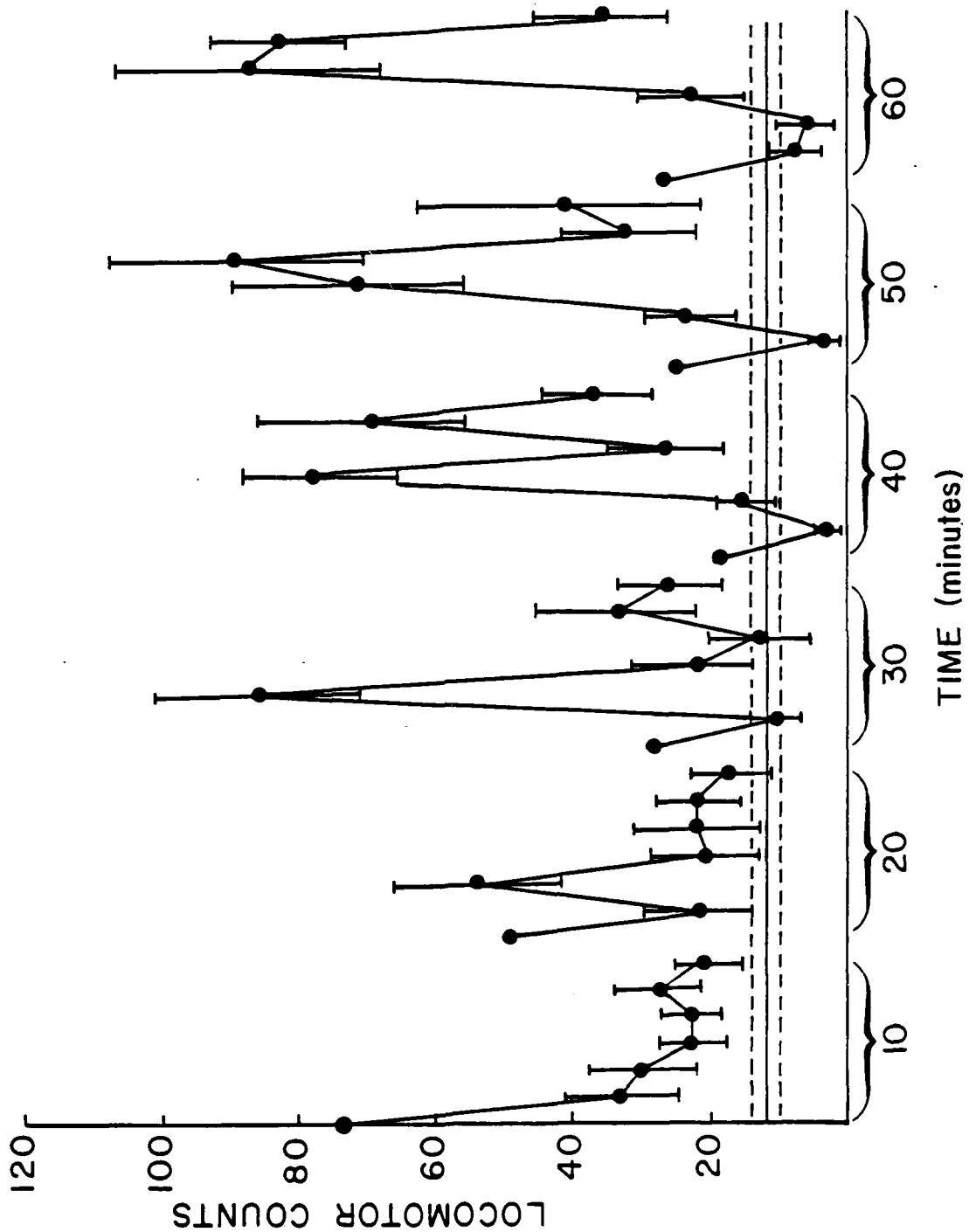

LOCOMOTOR COUNTS
120
100
80
60
40
20
10
20
30
40
50
60
TIME (minutes)

Figure 2. Dose-response data for apomorphine-induced locomotor activity in rats with bilateral 6-OHDA-induced lesions of the nucleus accumbens. Doses in each time period (left to right) are 0.025 mg/kg, 0.05, 0.1 and 0.2 mg/kg. There was an overall significant effect of treatment ($F(3,138) = 34.45$; $p < 0.01$), overall time effect ($F(5,138) = 12.06$; $p < 0.01$) and a dose by time interaction ($F(15,138) = 4.19$; $p < 0.01$).

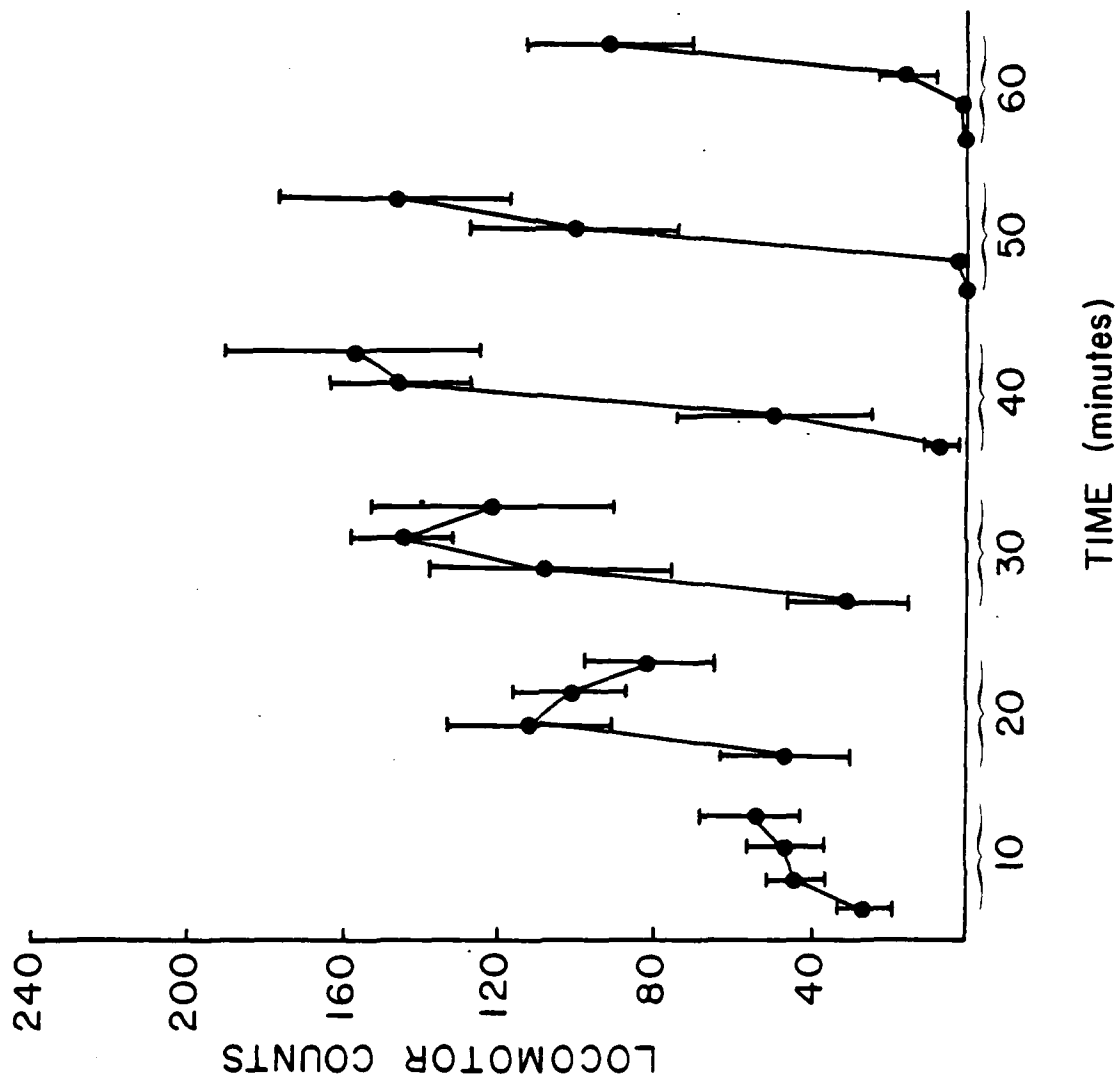

LOCOMOTOR COUNTS
240
200
160
120
80
40
10
20
30
40
50
60
TIME (minutes)

Figure 3. Total locomotor counts (light beam interruptions) induced by L-dopa/carbidopa over a 4 hour period (mean $\pm$ S.E.M. of 8 rats). Injections were administered subcutaneous. Activity increased with dose ($F(3,329) = 266.19$; $p < 0.01$) and there was a dose by time interaction ($F(33,329) = 7.37$; $p < 0.01$).

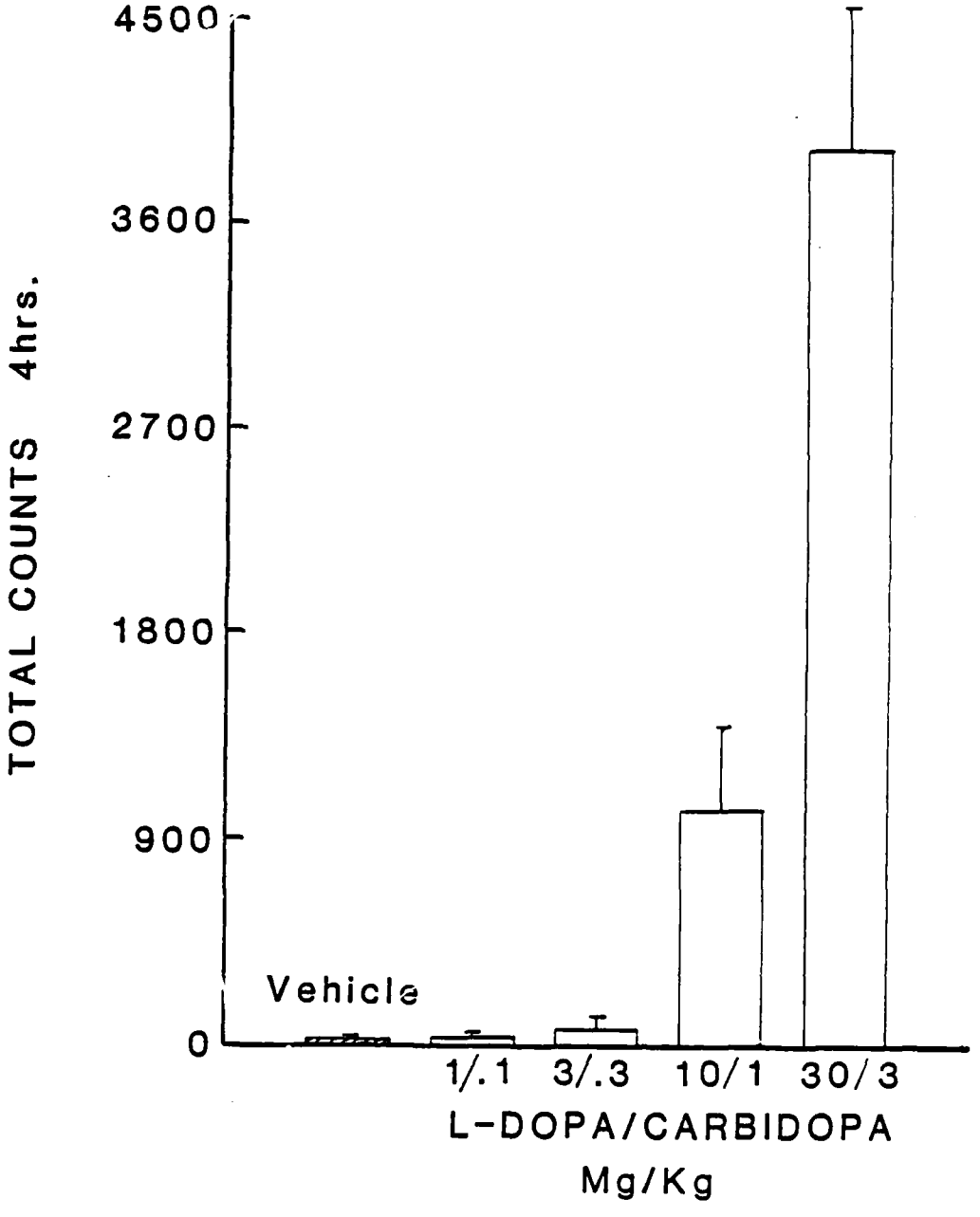

4500
3600
2700
1800
900
0
TOTAL COUNTS 4hrs.
Vehicle
1/.1
3/.3
10/1
30/3
L-DOPA/CARBIDOPA
Mg/Kg

Figure 4. Total locomotor counts (light beam interruptions) induced by lergotrile over an 8 hour period (mean $\pm$ S.E.M. of 8 rats). Injections were administered subcutaneous. Activity increased with dose ($F(3,329) = 33.26$; $p < 0.01$) and there was a dose by time interaction ($F(33,329) = 2.08$; $p < 0.01$).

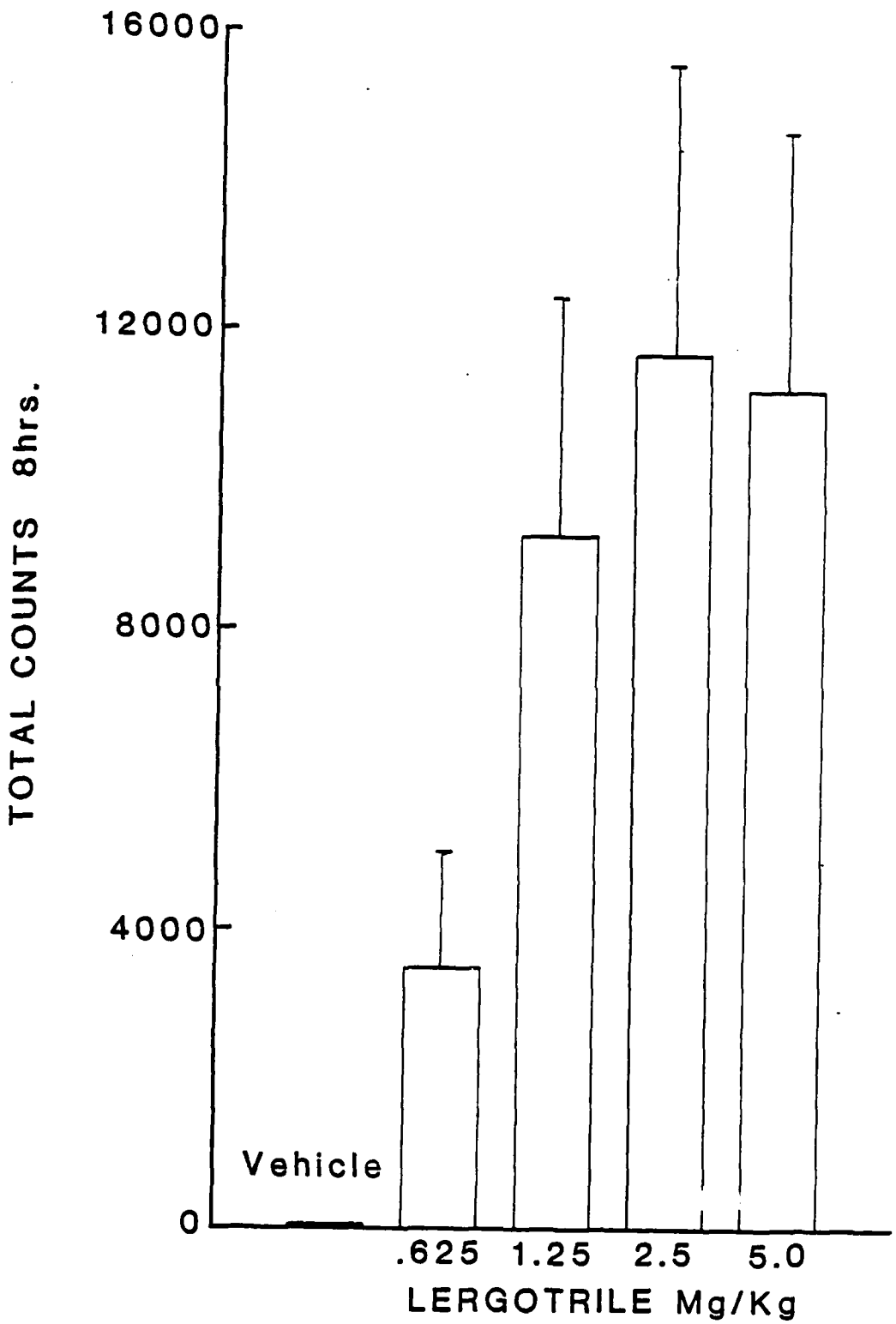

16000
12000
8000
4000
0
TOTAL COUNTS 8hrs.
Vehicle
.625
1.25
2.5
5.0
LERGOTRILE Mg/Kg

Figure 5. Total locomotor counts (light beam interruptions) induced by N-n-propylnorapomorphine over a 4 hour period (mean $\pm$ S.E.M. of 8 rats). Injections were administered subcutaneous. Activity increased with dose ($F(3,329) = 56.80$; $p < 0.01$) and there was a dose by time interaction ($F(33,329) = 3.24$; $p < 0.01$).

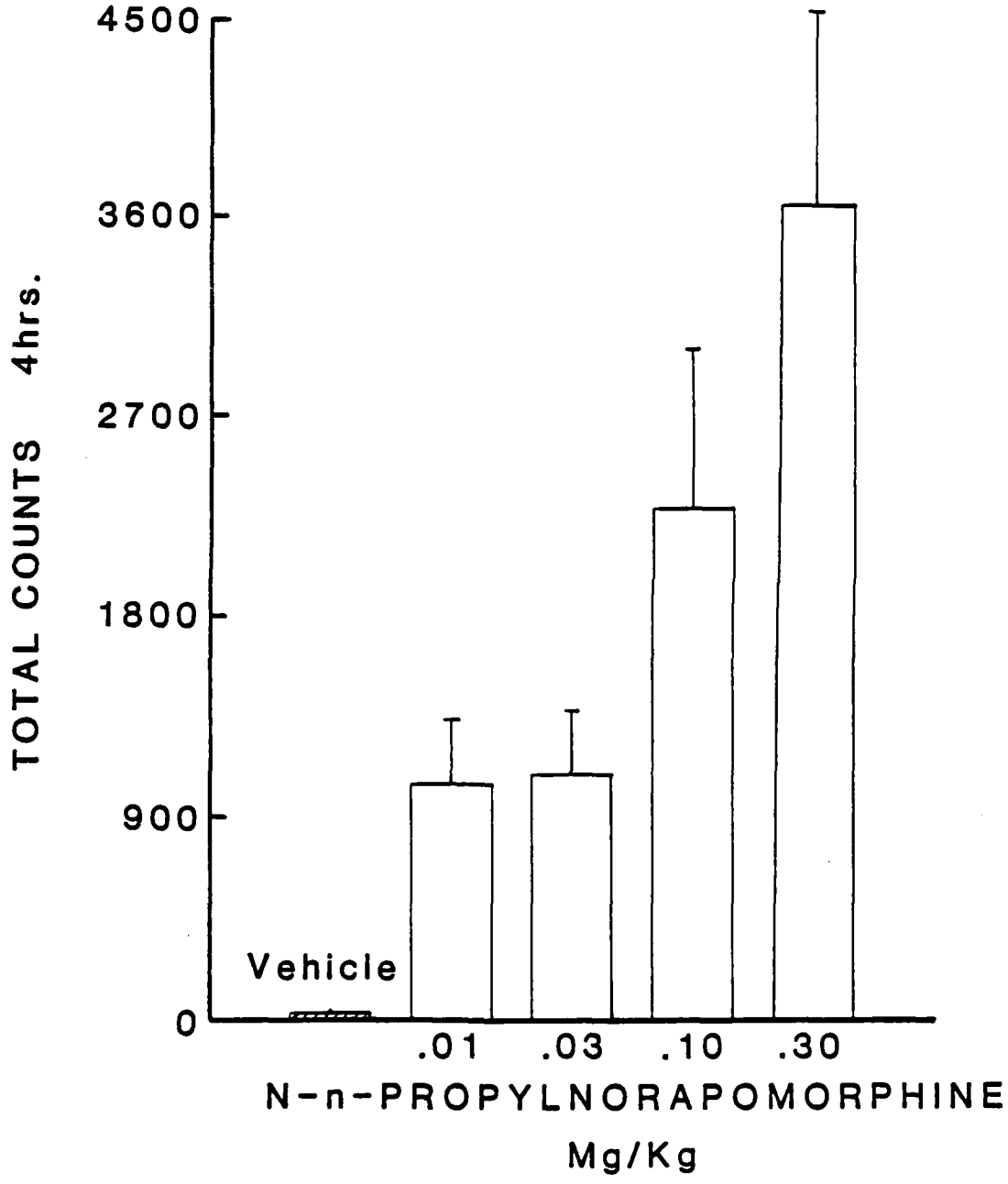

4500
3600
2700
1800
900
0
TOTAL COUNTS 4hrs.
Vehicle
.01
.03
.10
.30
N-n-PROPYLNORAPOMORPHINE
Mg/Kg

Figure 6. Total locomotor counts (light beam interruptions) induced by pergolide over a 6 hour period (mean $\pm$ S.E.M. of 8 rats). Injections were administered subcutaneous. Activity increased with dose ($F(3,329) = 34.35$; $p < 0.01$) while the dose by time interaction was non significant ($F(33,329) = 0.78$; $p > 0.05$). $ED_{50} = 0.056$.

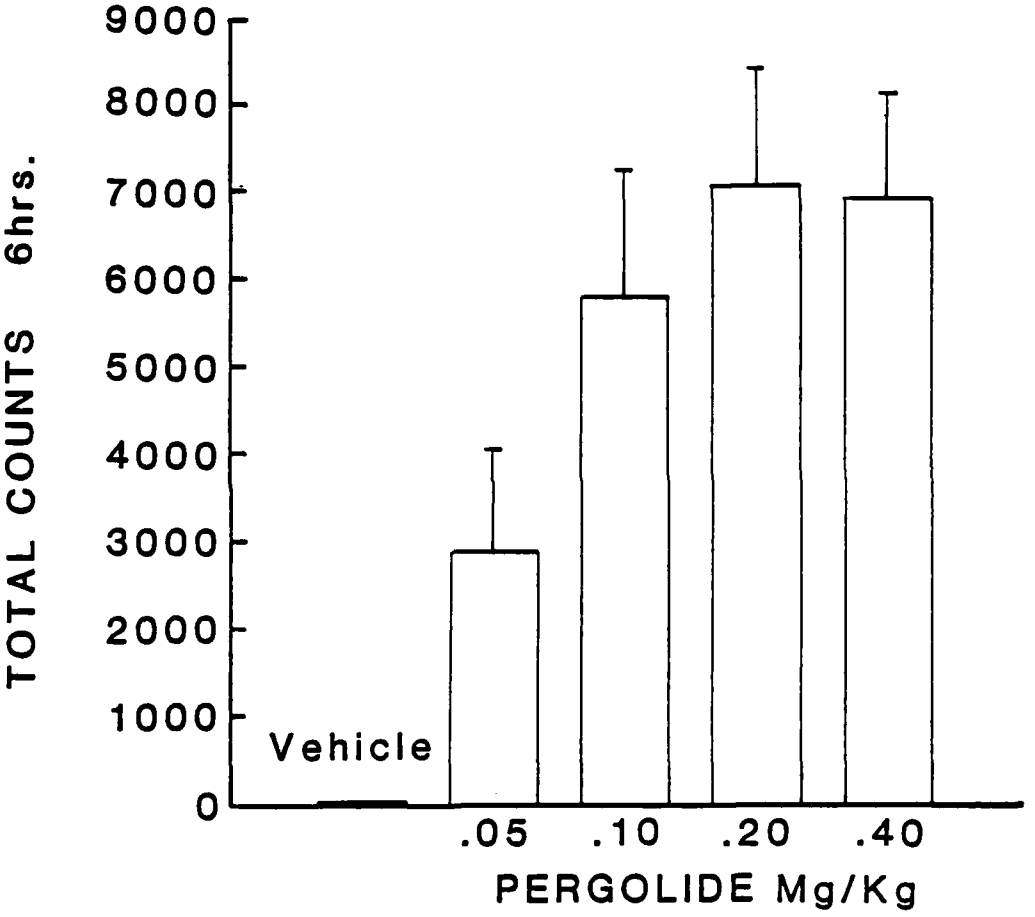

TOTAL COUNTS 6hrs.
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
Vehicle
.05
.10
.20
.40
PERGOLIDE Mg/Kg

Figure 7. Total locomotor counts (light beam interruptions) induced by piribedil over a 2.5 hour period (mean $\pm$ S.E.M. of 8 rats). Injections were administered subcutaneous. Activity increased with dose ($F(3,413) = 73.39$; $p < 0.01$) and there was a dose by time interaction ($F(42,413) = 3.32$; $p < 0.01$). ED_{50} = 1.31.

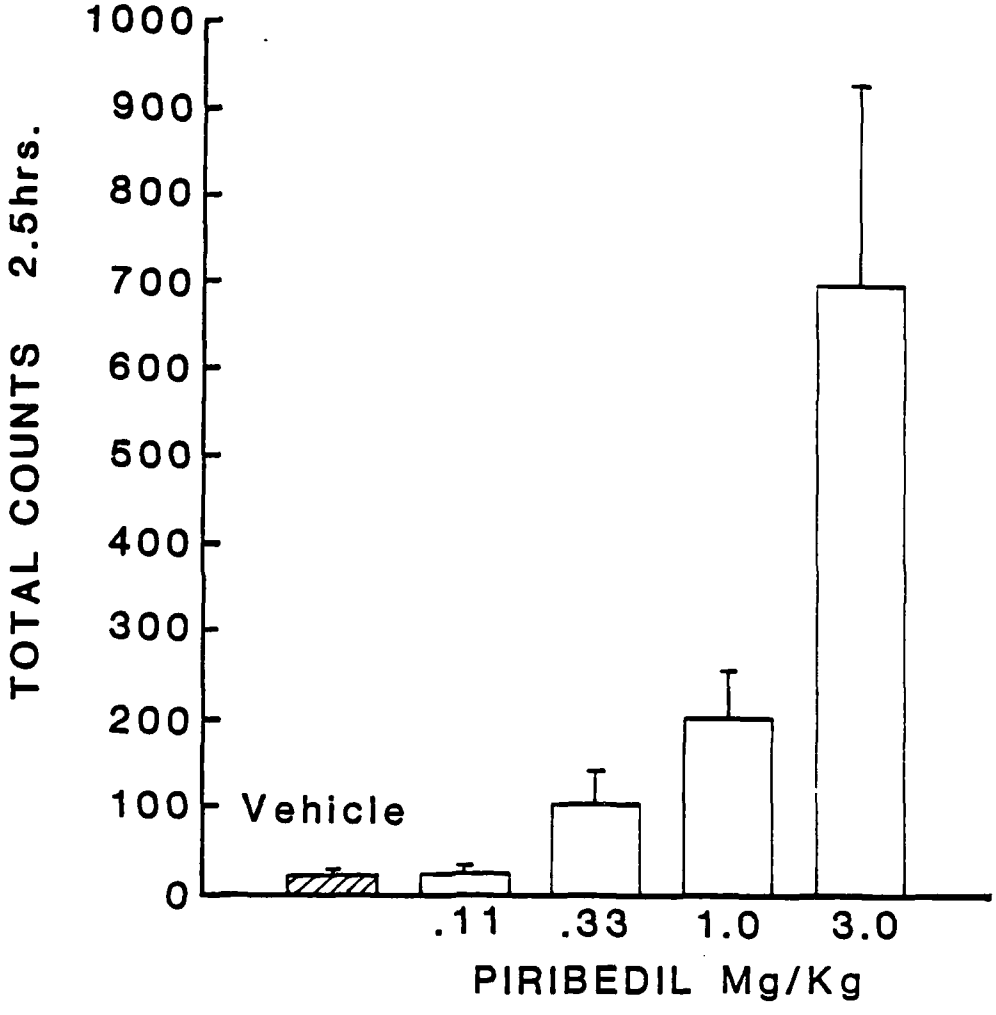
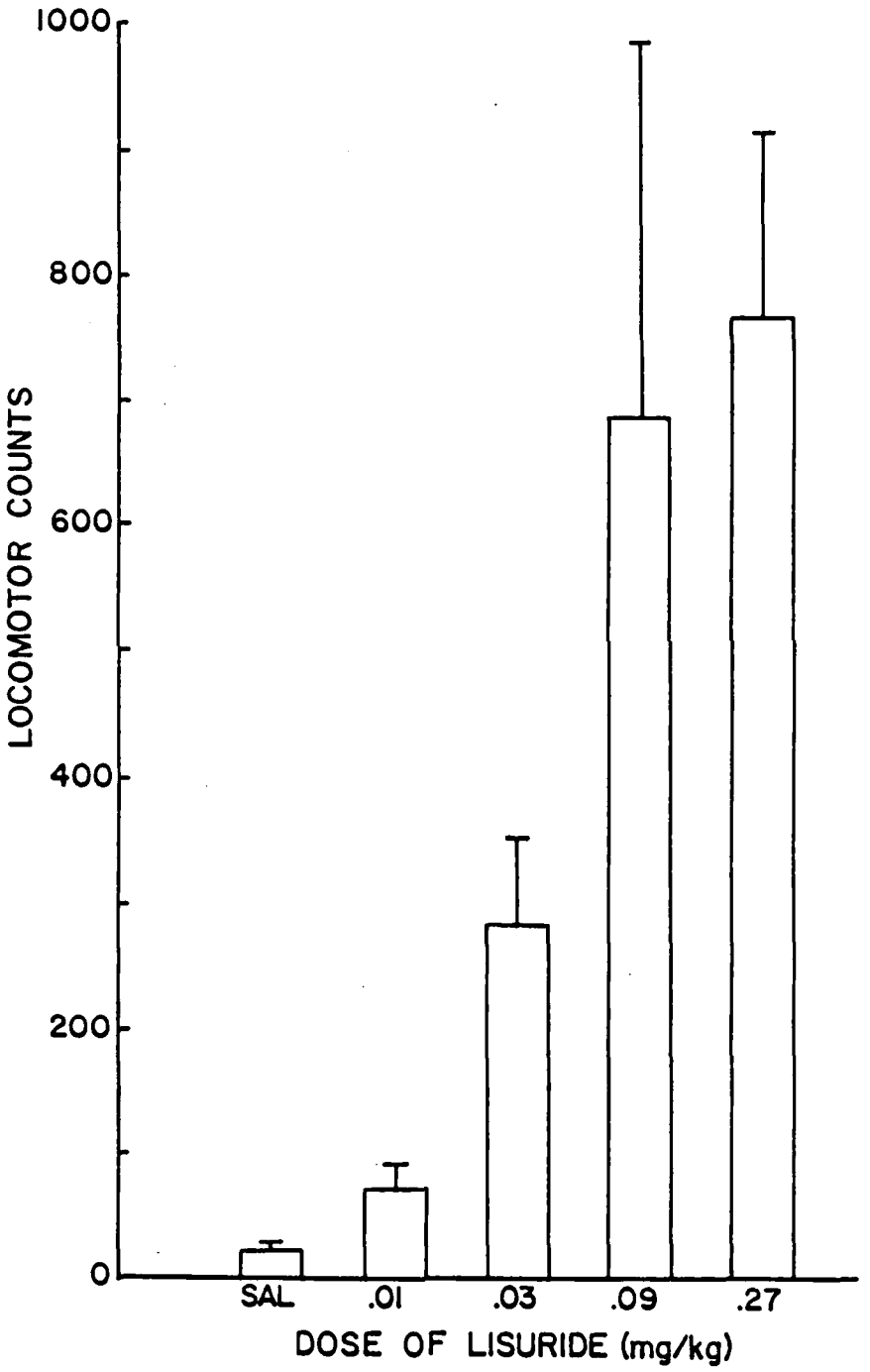

TOTAL COUNTS 2.5hrs.
1000
900
800
700
600
500
400
300
200
100
0
Vehicle
.11
.33
1.0
3.0
PIRIBEDIL Mg/Kg

Figure 8. Total locomotor counts (light beam interruptions) induced by lisuride over a 3 hour period (mean $\pm$ S.E.M. of 8 rats). Injections were administered subcutaneous. Activity increased with dose ($F(3,161) = 15.85$; $p < 0.01$) while the dose by time interaction was non significant ($F(15,161) = 0.81$; $p > 0.05$). $ED_{50} = 0.038$.


1000
800
600
400
200
0
LOCOMOTOR COUNTS
SAL
.01
.03
.09
.27
DOSE OF LISURIDE (mg/kg)

Effectiveness of 6-OHDA-induced lesions of the NAS

In the 8 groups of rats used to study dopamine agonist-induced locomotor hyperactivity, dopamine concentrations (as a per cent of control values) are presented in Table IV. Overall depletions for the groups were 73 ± 3 % in the olfactory tubercle, 74 ± 4 % in the NAS and 20 ± 2 % in the striatum. Interestingly, the correlation (r = 0.38) between peak locomotor activity caused by a screening dose of 0.1 mg/kg apomorphine and per cent depletion of dopamine in the NAS for each rat was not as strong as expected (n=64).

TABLE IV

Dopamine concentration (per cent of control)

Group	OT	NAS	STR
Apo	19 ± 7	28 ± 9	86 ± 8
L-dopa	21 ± 5	10 ± 2	79 ± 6
Lerg	36 ± 6	32 ± 7	89 ± 4
NPA	23 ± 5	25 ± 9	76 ± 7
Perg	42 ± 9	39 ± 10	81 ± 7
Pirib	21 ± 8	22 ± 6	78 ± 8
Lis	48 ± 7	36 ± 7	74 ± 9
Sal	6 ± 4	13 ± 5	73 ± 7

Apomorphine (Apo), n=8; L-dopa/carbidopa (L-dopa), n=7; Lergotrile (Lerg), n=8; N-n-propylnorapomorphine (NPA), n=8; Pergolide (perg), n=8; Piribedil (Pirib), n=8; Lisuride (Lis), n=8; Saline (Sal), n=4. Control (n=28) values were: olfactory tubercle 2.91 ± 0.28 ug/g, nucleus accumbens 4.11 ± 0.39 ug/g, striatum 5.45 ± 0.42 ug/g. Values are expressed as per cent of controls assayed in the same experiment.

Direct infusion of apomorphine or SKF 38393 into intact and dopamine depleted NAS

In Figures 9 and 10 it can be seen that direct infusion of apomorphine (10 ug) and SKF 38393 (15 ug), a purported D-1 agonist, into dopamine-depleted NAS caused a significant increase in locomotor activity compared to vehicle infusion. Peak locomotor counts (per 30 minute period) following infusion of apomorphine (788 $\pm$ 221, mean $\pm$ S.E.M.) and SKF 38393 (867 $\pm$ 211, mean $\pm$ S.E.M.) occurred at 1 hour and 4 hours, respectively. Infusion of apomorphine (10 ug) into intact NAS also significantly increased locomotor activity compared to vehicle infusion. As well, the difference between apomorphine infusion into normal and supersensitive NAS was significant. SKF 38393 infusions into intact NAS did not significantly increase locomotor activity (515 $\pm$ 186, mean $\pm$ S.E.M., counts for the 4 hour test period, n=7) compared to vehicle infusion for the same time period (176 $\pm$ 24, mean $\pm$ S.E.M.).

D. Discussion

The role of the nucleus accumbens in drug-induced locomotor hyperactivity has been confirmed in these studies. A variety of dopamine agonists were effective in producing locomotion in

Figure 9. Effects of intraaccumbens infusion of 10 ug apomorphine in animals with supersensitive and intact NAS, compared to vehicle infusion (cross-over, n = 6 each group). Animals with supersensitive NAS were more active than intact animals. Apomorphine groups differed significantly from vehicle infused controls ($F(1,8) = 13.8$; $p < 0.01$).

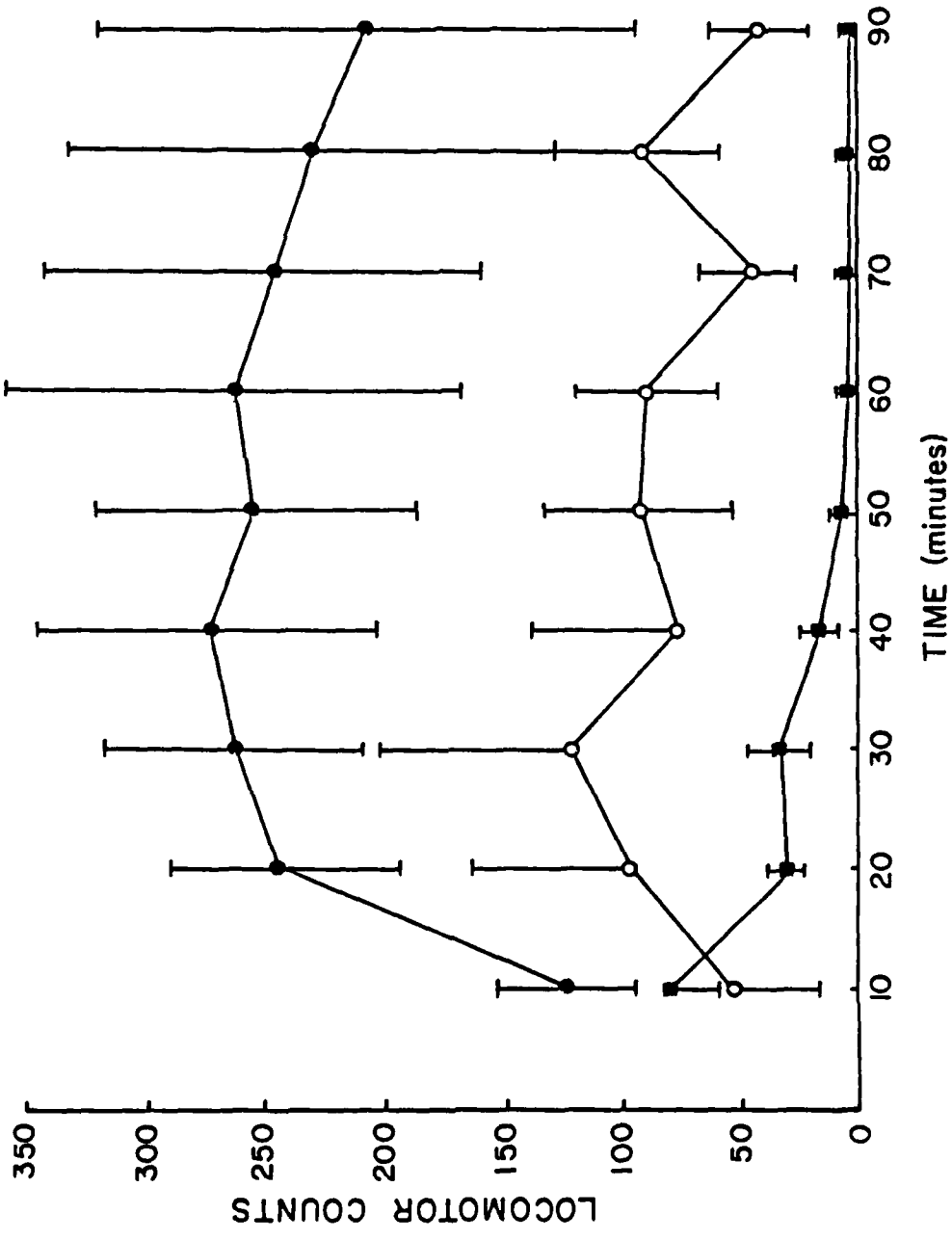
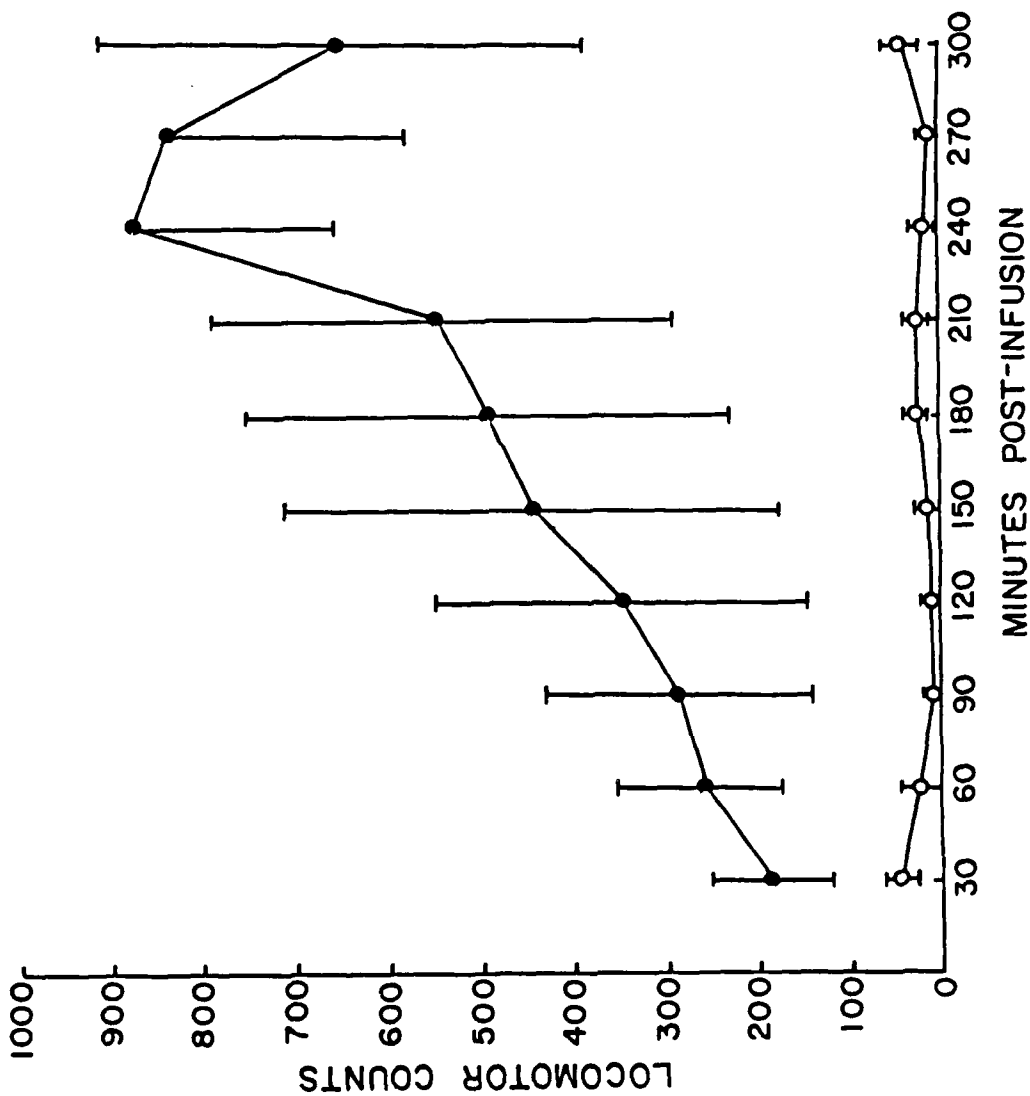

LOCOMOTOR COUNTS
350
300
250
200
150
100
50
0
10
20
30
40
50
60
70
80
90
TIME (minutes)

Figure 10. Effects of intraaccumbens SKF 38393 (15 ug) on locomotor activity in animals with supersensitive NAS compared to vehicle infusion (cross-over, n = 6 each group). Infusion of SKF 38393 differed significantly from vehicle infused controls ($F(1,95) = 74.88$; $p < 0.01$).


LOCOMOTOR COUNTS
1000
900
800
700
600
500
400
300
200
100
0
30
60
90
120
150
180
210
240
270
300
MINUTES POST-INFUSION

animals with bilateral 6-OHDA-induced lesions of the accumbens, lesions which depleted NAS dopamine by 74% while having mild effects on dopamine in the striatum (20% depletion). The overall behavior caused by each of these drugs appeared identical, i.e., occasional rearing, sniffing and frequent cage crossings.

The direct infusion of apomorphine and SKF 38393 into dopamine-depleted NAS also caused locomotor hyperactivity, but approximately two-fold higher compared to systemic injections. Both drugs produced similar maximum responses with that for apomorphine occuring at 1 hour and for SKF 38393 at 4 hours post infusion. Thus, a mixed dopamine agonist and a proposed D-1 specific agonist gave similar results when infused into dopamine-depleted NAS. Infusions of apomorphine into intact NAS also resulted in locomotor hyperactivity while SKF 38393 infusions did not. Others have noted inconsistent results with infusions of dopaminergic agonists into intact NAS, which could explain the lack of effect of SKF 38393 in this study (Van Rossum et al. 1977).

In normal animals, only a narrow dose range of apomorphine caused locomotor hyperactivity without stereotypic activity. A dose of 0.1 mg/kg was insufficient to cause locomotion (in fact decreased it), while 0.4 mg/kg and higher doses caused stereotypic behavior which interferred with the expression of locomotor hyperactivity. In this experiment (using a single infrared light beam across the long axis of the cage) only the dose of 0.2 mg/kg

apomorphine produced enhanced locomotor hyperactivity in the first 30 minutes. Other studies present conflicting data concerning apomorphine-induced locomotor activity in normal rats. Part of this conflict can be explained by the use of different types of activity monitoring devices. Some investigators have used actometers (which have stainless steel grid floors attached to a DC current generator) and report locomotor hyperactivity at doses of apomorphine in the range of 0.25 to 0.625 mg/kg (Montanaro et al. 1983). Others using devices similar to mine (except for multiple light beams) either report no facilitation of locomotion with apomorphine (Costall et al. 1977) or a general trend for all doses tested to cause increasing locomotion with peak effects occuring at 5.0 mg/kg (Fray et al. 1980). In the present study, doses of apomorphine that caused stereotypy in early stages of the drug effect, caused enhanced locomotion when the drug effect was in latter stages. Thus, whereas 0.2 mg/kg apomorphine gave a maximum response at 30 minutes, 0.4 mg/kg was at 40 minutes, 0.8 mg/kg at 50 min. and 1.6 mg/kg at 60 min.

Locomotor activity in these studies has been shown to be intimately associated with the nucleus accumbens. Thus, systemic injections in animals with supersensitive NAS and direct infusions into intact and supersensitive NAS resulted in locomotor hyperactivity. The narrow dose range for apomorphine-induced locomotor hyperactivity in control animals is interesting when compared to the effective dose range for amphetamine (which shows

a greater range). This may indicate a greater difference in effective dose ranges of amphetamine for the two behavioral responses. Thus, locomotor activity is expressed over a wider dose range with little interference by stereotypic behavior. If as these and and other data suggest, locomotor activity and stereotypic activity reflect dopamine stimulation in accumbens and striatum respectiviely, the emergence of the two behaviors at different relative doses may reflect this anatomical relationship.

In the next section, a further difference in apomorphine-induced behaviors between the NAS and striatum will be examined. Whereas apomorphine administration in animals with supersensitive NAS resulted in amplified locomotor activity, apomorphine in animals with bilaterally supersensitive striata did not result in a clear amplification of striatally-mediated stereotypy.

IV. NIGROSTRIATAL SYSTEM

A. Introduction

The nigrostriatal dopamine pathway in the rat has been associated with drug-induced stereotypic behavior. This drug-induced stereotypy is characterized by a continuous repetition of behavioral patterns to an exclusion of normal behaviors, such as grooming, eating and drinking (Randrup et al. 1963; Fog et al. 1966ab; Ernst 1967). In a review of stereotypic behavior, Fog (1972) described the effects in rats of 10 mg/kg d-amphetamine: "-----5-10 minutes after injection, sniffing in the air and of the walls and bottom of the cage starts. The sniffing increases and becomes accompanied by licking and biting at the wire netting. The locomotion decreases along with other normal activities such as grooming, eating and drinking, and is totally absent after 30-40 min. following the amphetamine injection. The stereotypy phase begins thereafter, reaches its maximum after 1 hour and ceases 2 to 3 hours later. It is characterized by continuous sniffing, licking and biting at the wires covering only a small area of the cage floor. Forward locomotion is absent--only bursts of backward locomotion are occasionally seen." The preferential involvement of the striatum in this behavior has

been confirmed by both infusions of neuroleptics into the striatum to block systemic amphetamine-induced stereotypy (Fog et al. 1968, 1971) and by direct infusion of dopaminergic agonists into the striatum to produce stereotypy (Costall et al. 1980; Costall and Naylor 1981; Joyce 1983). Other transmitters closely associated with striatal dopamine can also modify drug-induced stereotypy. Thus, anticholinergic drugs amplify amphetamine-induced stereotypy (Fog et al. 1966ab; Fog 1967) while cholinergic agonists block apomorphine and amphetamine-induced stereotypy (Gonzalez and Elinwood, 1984). GABA-ergic agonists also possess the ability to block amphetamine and apomorphine-induced stereotypy (Ellinwood et al. 1983). Stereotypic behavior can also be elicited by stimulation of structures efferent to the striatum. Gnawing and licking was noted following infusion of dopamine into the globus pallidus, and by muscimol (a GABA receptor agonist) infused in the substantia nigra pars reticulata (Joyce 1983; Olianas 1978). As well, gnawing behavior has been observed following infusion of picrotoxin into the dorsal mesencephalic reticular formation and the deep layers of the superior colliculus (DiChiara et al. 1981; Redgrave et al. 1981).

The main objective of this section is to study the effects of dopamine agonists in animals with bilateral 6-OHDA-induced lesions of the striata (to determine whether denervation will specifically accentuate striatally-mediated behavior). Unilateral destruction of the nigro-striatal dopamine pathway by 6-OHDA has been used

extensively to study the effects of direct and indirect dopamine agonists on rotational behavior in rodents. Very few studies have examined drug-induced behaviors following bilateral lesions. Although increases in the intensity of apomorphine-induced stereotypic activity have been described after bilateral lesions (Schoenfeld and Uretsky 1972; Creese and Iversen 1973), it has not been quantitatively evaluated. Estimates of lesion-induced supersensitization using a rotational model in rats and mice with striato-nigral electrolytic lesions are as great as thirty fold (Marshall and Ungerstedt 1977; Mandel and Randall 1985) In contrast, supersensitization of stereotypic activity utilizing chronic neuroleptics results in an apparent 2 fold shift to the left (Randall and Randall, in prep) of the dose response curve, even though increments in dopamine receptor number are roughly comparable (Creese et al. 1977; Burt et al. 1977).

A number of investigators have noted stereotypic grooming and self-mutilation in bilaterally or even unilaterally 6-OHDA lesioned rats (Ungerstedt 1971; Price and Fibiger 1974; Marshall and Ungerstedt 1977). Breese (1984) also reported stereotypic grooming in adult rats which received intraventricular 6-OHDA as neonates. This behavior is not observed after acute apomorphine treatment in intact animals.

It is important to determine whether altered forms of apomorphine-induced behavior in supersensitized animals might represent simply an extreme intensification of the normal

response. Alterations in the quality of the response are indicative of a much more complex effect of denervation than simple supersensitization. This study will utilize lesions which specifically deplete dopamine in the striatum without affecting the NAS.

B. Experimental Design

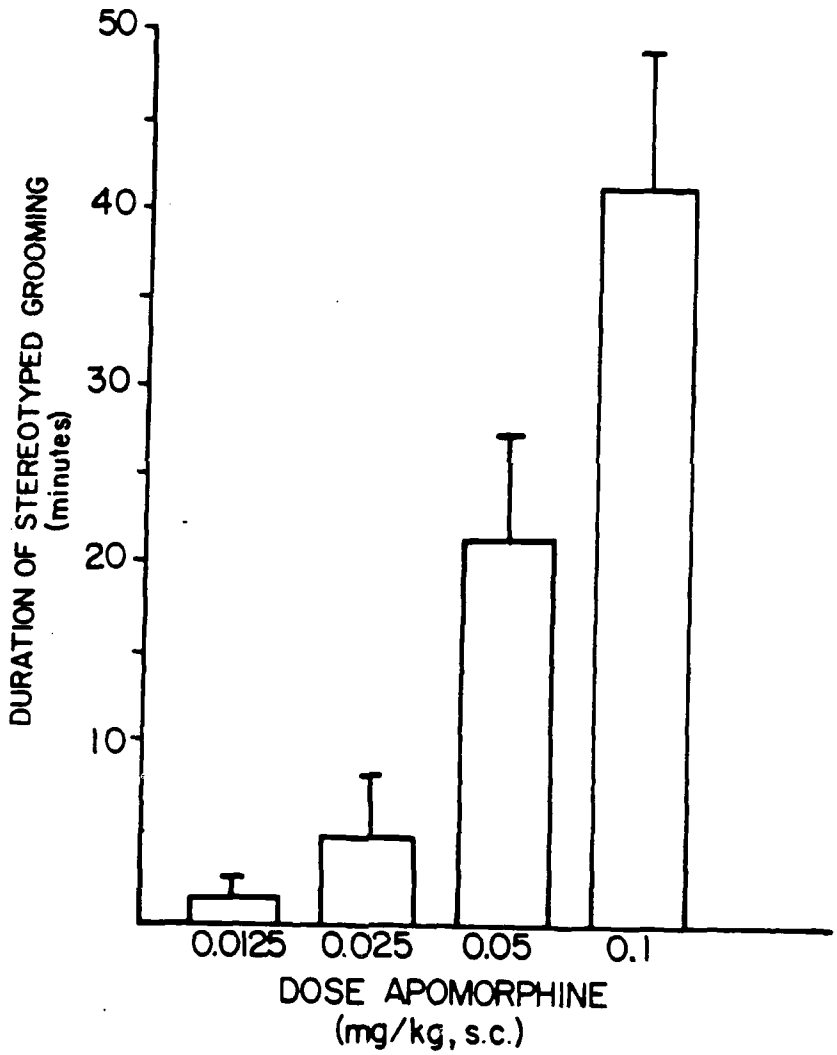
Dose response curves for apomorphine in animals with bilateral lesions of the striatum, in intact animals and in intact, food deprived animals were derived from experimental designs using balanced Latin Squares. In this design, there were 4 doses of apomorphine administered to each animal (n=8) over a period of 4 weeks (4 x 4, 2 replicates). Every dose followed every other dose, with the last day repeated 1 week later.

C. Results

Stereotypic grooming following systemic injections of dopaminergic agents.

Animals with bilateral 6-OHDA-induced lesions of the nigro-striatal pathway failed to show the normal pattern of apomorphine-induced stereotypic behavior. Instead, the predominate response was grooming-like behavior which at higher

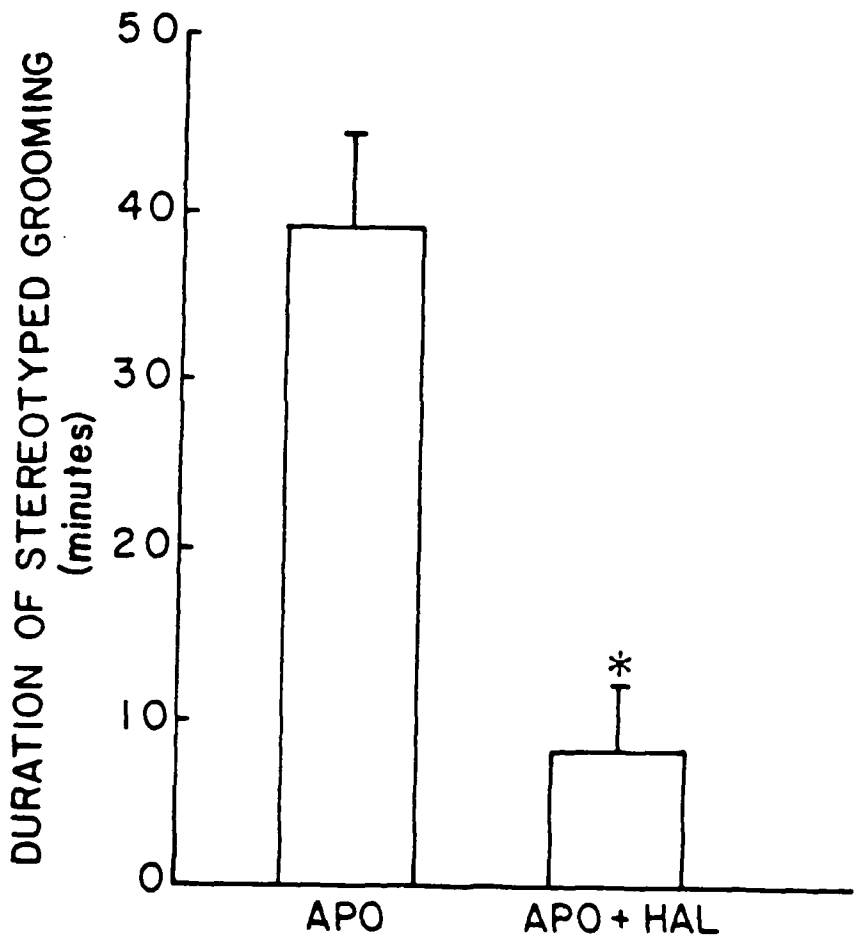
Figure 11. Dose-response for apomorphine-induced stereotypic grooming. ANOVA: dose, $p<0.01$; log-linear, $p<0.01$, with no significant departure, $p>0.10$. Mean $\pm$ S.E.M, n=8, balanced Latin Square.


50
40
30
20
10
DURATION OF STEREOTYPED GROOMING
(minutes)
0.0125
0.025
0.05
0.1
DOSE APOMORPHINE
(mg/kg, s.c.)

doses became self-injurious. Stereotypic grooming behavior in most animals was directed at the forepaws, however, other parts of the forelimbs, the rear paws and flanks were sometimes involved. Animals would typically assume a posture of normal facial grooming with the forepaws held close to the mouth, but then instead of running the paws over the snout and attending to other body parts (as is typical in normal grooming), the animals would remain frozen for up to 40 minutes mouthing their paws. At higher doses of apomorphine, biting was more intense and usually resulted in tissue damage. The ED_{50} for stereotypic grooming was 0.034 mg/kg (Figure 11). In intact animals much higher doses of apomorphine (15 to 60 mg/kg) never caused self directed gnawing or licking behavior. The ED_{50} for the appearance of biting (at the walls of the enclosure) in intact animals was 0.3 mg/kg. Other dopamine agonists also produced stereotypic grooming in animals with bilateral striatal lesions(identical to apomorphine-induced stereotypic grooming). L-dopa/carbidopa (30:3 and 10:1 mg/kg) caused stereotypic grooming that lasted for 67.5 $\pm$ 12.5 minutes (mean $\pm$ S.E.M., n=2 each dose, averaged over 2 doses), N-n-propylnorapomorphine (1.0, 0.25 and 0.05 mg/kg) for 65 $\pm$ 13.6 minutes (n=2 each dose, averaged over 3 doses), pergolide (1.0, 0.25 and 0.05 mg/kg) for 53.3 $\pm$ 10.5 minutes (n=2 each dose, averaged over 3 doses) and bromocriptine (10 mg/kg) for 25 $\pm$ 8.7 minutes (n=4)

The stereotypic grooming produced by systemic apomorphine is

Figure 12. Effects of haloperidol (0.5 mg/kg) or vehicle on apomorphine-induced (0.3 mg/kg) stereotypic grooming. *$p<0.05$, Mann-Whitney U test. Mean $\pm$ S.E.M., n=5, cross-over design.


DURATION OF STEREOTYPED GROOMING
(minutes)
50
40
30
20
10
0
*
APO
APO + HAL

sensitive to haloperidol. Animals administered haloperidol (0.5 mg/kg) 2 hours prior to apomorphine (0.3 mg/kg) showed a significant reduction in stereotypic grooming compared to vehicle controls (Figure 12).

Correlation between dopamine depletion, weight loss and stereotypic grooming.

Body weight loss and stereotypic grooming were highly correlated with dopamine depletion in animals with lesions (Figures 13,14). However, weight loss caused by 6-OHDA-induced lesions is not a contributing factor to this behavior, since food-deprived controls with comparable weight loss did not exhibit stereotypic grooming.

Direct bilateral infusion of dopaminergic agents into denervated striata.

Apomorphine (10 ug) infused bilaterally caused stereotypic grooming qualitatively similar to systemic injections. In Figure 15, the total time spent in stereotypic grooming behavior following apomorphine (21 $\pm$ 4 minutes, mean $\pm$ S.E.M.) is compared to vehicle infusion which did not cause this behavior. In another group of rats, the effects of SCH 23390 (1ug) or sulpiride (1ug) infused 30 minutes prior to the infusion of 10 ug

Figure 13. Correlation between body weight (10 days after lesion) and striatal dopamine depletion, n=16.

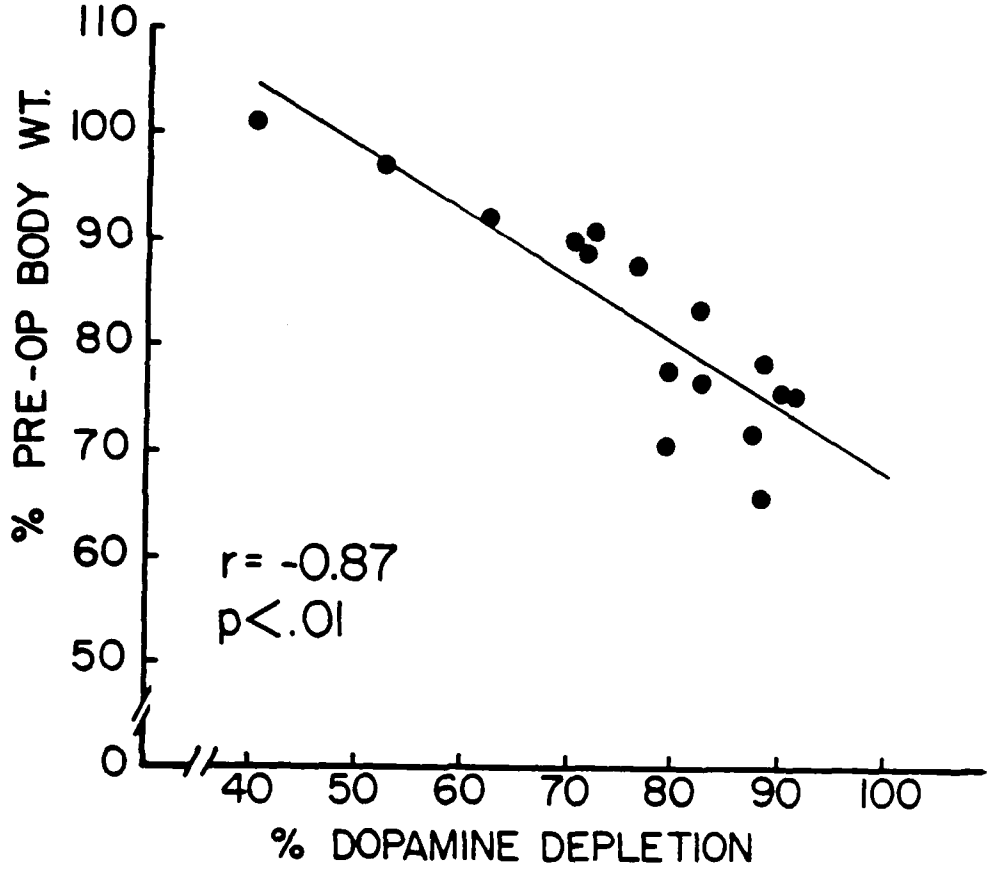

110
100
90
80
70
60
50
0
% PRE-OP BODY WT.
r= -0.87
p<.01
40
50
60
70
80
90
100
% DOPAMINE DEPLETION

Figure 14. Correlation between stereotypic grooming and dopamine depletion, n=8. Points represent total duration of stereotypic grooming across 4 doses of apomorphine.

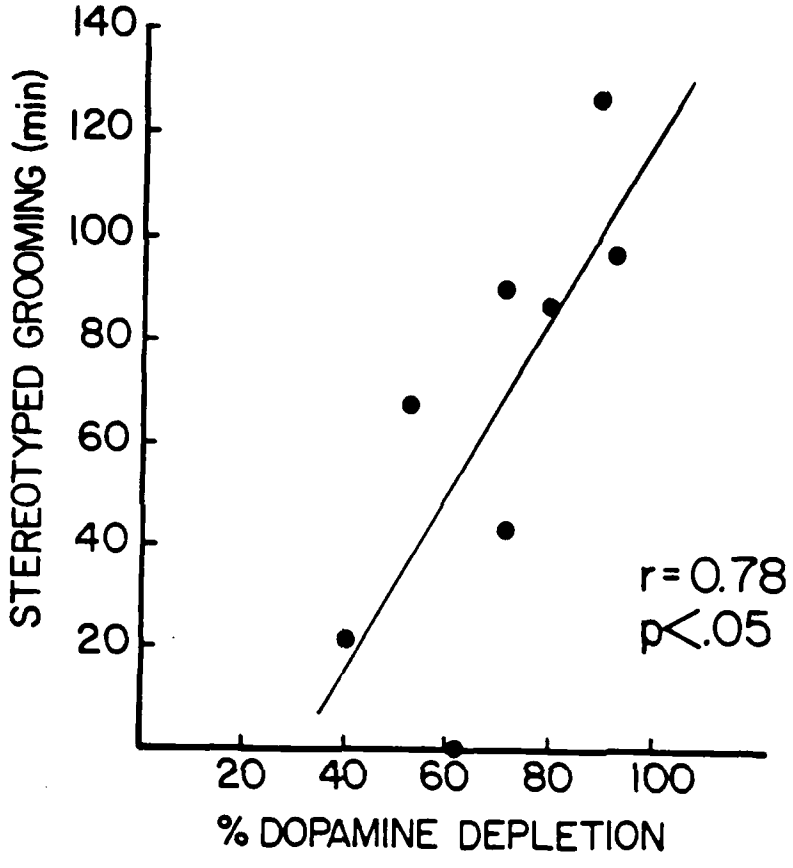
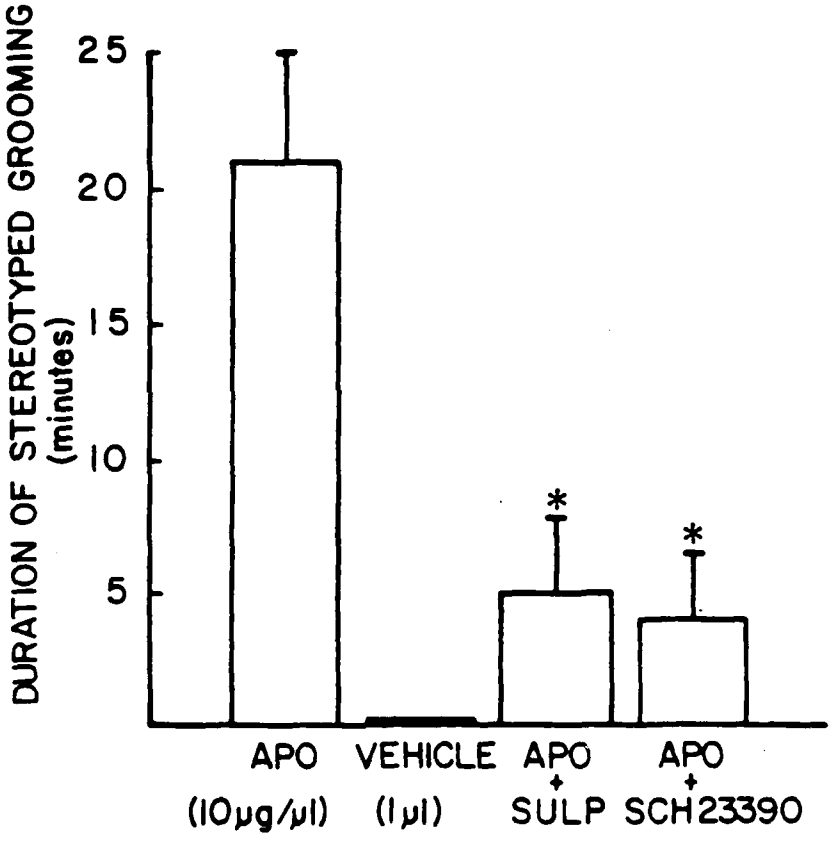

140
120
100
80
60
40
20
STEREOTYPED GROOMING (min)
20
40
60
80
100
% DOPAMINE DEPLETION
r=0.78
p<.05

Figure 15. Effects of intrastriatal apomorphine (n=12) or vehicle (n=4) in bilateral denervated striata. Intrastriatal sulpiride (1 ug,n=11) and SCH 23390 (1 ug,n=11) reduced intrastriatal apomorphine-induced stereotypic grooming, *$p<0.01$, Mann-Whitney U test, Mean $\pm$ S.E.M., cross-over design.


DURATION OF STEREOTYPED GROOMING (minutes)
25
20
15
10
5
*
*
APO (10µg/µl)
VEHICLE (1µl)
APO + SULP
APO + SCH23390

apomorphine is also presented (Figure 15). Both dopamine antagonists decreased stereotypic grooming time, SCH 23390 by 81% and sulpiride by 76% (no significant differences between compounds at this dose).

Infusion of SKF 38393 (30 ug) produced a qualitatively different stereotyped behavior (which was self-directed) compared to apomorphine infusion. Whereas apomorphine-induced behaviors were predominantly directed toward the forepaws, SKF 38393 behaviors were directed toward the flanks and genital regions. The time course of SKF 38393 was long (> 4 hrs.) but in 4 of the 6 animals tested there was a delay of approximately 2 hours after the infusion before behavioral arousal occurred.

Biochemical data

Regional assay data for animals used to derive the ED_{50} for apomorphine-induced stereotypic grooming (n=8) and for animals used in testing other dopamine agonists (n=8) is presented in Table V. Animals were sacrificed approximately 1 month following surgery. Lesions produced a significant (81%) depletion of dopamine in the striatum while having non-significant effects in the nucleus accumbens (7%) and olfactory tubercle (25%).

Table V.

Dopamine Values (ug/g)

	OT	NAS	STR
Controls (n=8)	1.12 ± 0.22	1.36 ± 0.17	2.61 ± 0.40
6-OHDA lesion (n=16)	0.84 ± 0.10	1.27 ± 0.08	0.49 ± 0.08*
% control	75% n.s.	93% n.s.	19%

OT (olfactory tubercle), NAS (nucleus accumbens), STR (striatum)
* p <0.01 (Mann-Whitney U test) compared to striatum of controls.

D. Discussion

Administration of dopamine agonists to rats with bilateral 6-OHDA-induced lesions of the nigro-striatal dopamine pathway invariably caused stereotypic grooming (for forty minutes or more with little intervening behavior). This behavior was characterized by mouthing of body parts, especially of the forepaws and forelimbs, with self-mutilation occurring at higher doses of agonists. Stereotypic grooming was an unexpected behavior, as we originally intended to study the effects of various dopamine agonists in causing stereotypy following dopamine depletion. Instead of observing an amplification of typical amphetamine- or apomorphine-induced stereotypy, an entirely unique behavior

emerged.

Stereotypic grooming following bilateral 6-OHDA lesions appears to be a true alteration in the form of apomorphine-induced behavior rather than simply a very intense form of the drug-induced behavior in unlesioned animals. First, unlesioned rats fail to show the stereotypic grooming response even at very high doses (up to 60 mg/kg) of apomorphine. Secondly, the striatal-dopamine depleted rats failed to show typical stereotypic activity (sniffing, head weaving, etc.) at doses below those at which stereotypic grooming is observed (0.0125 mg/kg). The disappearance of normal stereotypic behavior may result from response incompatibiltiy, i.e., stereotypic grooming itself blocks normal stereotypic behavior. If this is the case, the ED_{50} for stereotypic behavior in the denervated rat must be considerably higher than that for the grooming response.

The caudate nucleus seems to be the primary structure involved in stereotypic grooming since the lesions were specific to this nucleus and because local infusion of apomorphine into the caudate was as effective as systemic injection. Interestingly, the posture assumed by the rats closely resembles postures used during feeding (when food is held with the forepaws) or normal facial grooming. In this regard both aphagia (following lesions of the ascending nigro-striatal dopamine pathway) and grooming (induced by intraventricular ACTH) have been associated with the caudate nucleus. One study, using rats with recent (24-48 hours

previously) bilateral 6-OHDA-induced lesions of the dopamine pathways, noted reversal of aphagia and akinesia by apomorphine (0.1 mg/kg sc) (Ljungberg and Ungerstedt 1976). These animals were noted to grasp food pellets in their forepaws and eat, maintaining this posture for 15-20 minutes and then slowly reverted back to akinesia. Thus, administration of apomorphine appears to release motoric components of eating behavior.

Although the striatal origins of stereotypic grooming seem clear, the pharmacological specificity of this response is not. The stereotypic grooming induced by dopamine agonists appears to be antagonized by both D1 and D2 agents. This may in part be due to the dose of antagonists used in this study, as current work in this laboratory (Yurek and Randall in preparation) indicate that extremely low doses of antagonists are needed to differentiate dopamine sub-type mediated behaviors. However, there was a difference noted in behavior when SKF 38393 (selective D1 agonist) or apomorphine was infused into the caudate nucleus. Whereas apomorphine behaviors were focused on the forepaws and included much biting, SKF 38393 behaviors were directed at the flanks and abdominal areas and included more licking. Systemic SKF 38393 has also been reported to cause prominent grooming behavior directed into the body in rats without prior lesion (Molloy and Waddington 1984). This behavior was antagonized by SCH 23390, but not by metoclopramide (specific D2 antagonist).

Substances such as ACTH and morphine can also induce

grooming-like responses in rats, apparently requiring intact dopamine pathways. The grooming induced by intraventricular (ICV) ACTH is of much shorter duration and less focused compared to the behavior observed in the present studies (Gispen et al. 1975). ACTH-induced grooming can be blocked by systemic haloperidol (Guild and Dunn 1982) or by infusion of haloperidol into the caudate nucleus (Wiegant et al. 1977). Naloxone (systemic) was also noted to block ICV ACTH-induced excessive grooming (Gispen and Isaacson 1981), suggesting the involvement of the opiate system in grooming behavior. This has been confirmed by the grooming induced by systemic and ICV infusions of morphine (Ayan and Randrup 1973; Gispen and Isaacson 1981). Morphine-induced grooming also seems to be dependent on intact dopamine pathways (Ayan and Randrup 1973). Of interest to this study, it has also been noted that chronic morphine administration in rats results in the onset of self-mutilation, especially of the forepaws (Fog 1970; Leander et al. 1975; Charness et al. 1975; Lucot et al. 1979).

Other studies have used bilateral 6-OHDA-induced lesions of the dopamine pathways and also reported self-directed biting and mutilation (Ungerstedt 1971; Price and Fibiger 1974). Neonates treated with intraventricular or intracisternal 6-OHDA self mutilate when challenged with apomorphine as adults (Creese and Iversen 1973; Breese et al. 1984). Interestingly, adult animals administered 6-OHDA using the same techniques do not self-mutilate

to apomorphine challenge (Schoenfeld and Uretsky 1972; Breese et al. 1984). The occurence of self-mutilation in rats following 6-OHDA has prompted comparisons of this behavior with the human disorder Lesch-Nyhan syndrome. This disorder is characterized by involuntary movement, self-mutilation (especially of the fingers and lips) and decreased dopamine markers in the basal ganglia (Lesch and Nyhan 1964; Lloyd et al. 1981).

Self-mutilation can be produced in rodents by other agents without prior dopamine depletion (see Baumeister and Frye 1984). Generally these agents were administered chronically and systemically, although there was one report of self-mutilation following infusion of 5'N ethylcarboxamide adenosine into the striatum followed by systemic apomorphine (Green et al. 1982). Also, local infusion of muscimol into the substantia nigra pars reticulata and picrotoxin into the superior colliculus, systems distal to the striatum, result in self-biting (Scheel-Kruger et al. 1977c; Redgrave et al. 1981; Taha et al. 1982; Baumeister and Frye 1984).

It is unclear why intraventricular (ICV) 6-OHDA in adults does not cause stereotypic grooming. One possibility is that some striatal regions, most likely near the globus pallidus (GP), were depleted to a lesser extent by ICV 6-OHDA. Our 6-OHDA lesions are made in the tail of the caudate, near the GP. These regions have been reported to selectively cause biting behaviors when dopamine agonists have been directly infused (Joyce 1983). ICV 6-OHDA in

neonates may lead to a more complete depletion of dopamine (Erinoff et al. 1984). Consistent with this is the high degree of stereotypic grooming in animals receiving ICV 6-OHDA as neonates (tested as adults) (Breese et al. 1984).

The character of drug-induced responses following dopamine depletion suggests caution in the interpretation of dose-response data based on univariate or automated data collection. Direct observation is a valuable adjunct to automated procedures (Rebec and Bashore 1984; DiChiara and Morelli 1984).

V. MESOLIMBIC AND NIGROSTRIATAL INTERACTIONS

A. General introduction

The two major dopamine containing structures in the brain (the NAS and striatum) have particular, drug-induced behaviors associated with them. Whereas locomotor activity seems to be the predominant motor behavior associated with the NAS, stereotypic behavior is the major motor behavior of the striatum. Few studies have examined instances where the NAS and striatum interact to either enhance or diminish a particular behavior. In this section three motor behaviors will be examined to test interactions of the NAS and striatum: circling, after lesions of the nigrostriatal pathway (experiment 1) and after lesions of the striatonigral pathway (experiment 2), locomotor hyperactivity (experiment 3) and stereotypic grooming (experiment 4).

Since locomotor hyperactivity and stereotypic grooming were covered in depth in the preceding two sections, the introduction for each of these behaviors will be brief.

B. Experiment 1: circling, nigrostriatal model

1. Introduction

The drug-induced rotation of rats with unilateral lesions of the nigrostriatal dopaminergic pathway (Ungerstedt and Arbuthnott 1970; Ungerstedt 71a,b) has served as a useful, simplified model for investigating the brain mechanmisms involved in motor function (Pycock 1980). Circling behavior is thought to result from a functional imbalance between ascending dopaminergic nigrostriatal pathways in the left and right brain hemispheres (Ungerstedt and Arbuthnott 1970; Arbuthnott and Crow 1971; Crow 1971; Ungerstedt 1971a; Costall et al. 1972). Rats with 6-OHDA-induced lesions of the striatum or substantia nigra turn ipsilateral to the lesion side following amphetamine administration and contralateral with apomorphine administration. The amphetamine-induced turning is caused by an increased release of dopamine from nigrostriatal terminals in the intact side, while apomorphine stimulates supersensitive dopamine receptors on the lesion side (Anden et al. 1966b; Ungerstedt and Arbuthnott 1970; Crow 1971; Christie and Crow 1971; Ungerstedt 1971ab; Christie and Crow 1973; Von Voigtlander and Moore 1973). After electrolytic lesions of the striatum, both amphetamine and apomorphine cause ipsilateral turning to the lesion side, since both dopaminergic nerve endings and dopamine receptors have been destroyed .

Activity at mesolimbic dopaminergic terminals also influences circling behavior. On the basis of observations that amphetamine-induced circling is blocked by destruction of the mesolimbic dopamine system (Kelly and Moore 1976; Kelly and Moore 1977; Pycock and Marsden 1978) or by injections of a dopamine antagonist directly into the NAS (Kelly and Moore 1977), it has been proposed that mesolimbic dopaminergic activity modulates this behavior as if by altering the gain of an amplifier involved in translating nigrostriatal dopaminergic activity into behavior (Kelly 1977; Moore and Kelly 1978). From these studies it can be seen that drug-induced circling behavior provides the best example of cooperation between the NAS and striatum. The striatum has been proposed to provide the postural component of circling, while the NAS provides the locomotion (Kelly and Moore 1977; Pycock and Marsden 1978). This hypothesis rests on studies linking each structure with only one of the two essential ingredients necessary for circling. For example, unilateral 6-OHDA-induced lesions of the NAS do not cause drug-induced postural assymetry (Kelly 1975), while unilateral lesions of the striatum do (Anden et al. 1966b). Direct unilateral infusions of dopamine or dopaminergic agonists into the striatum (Costall et al. 1974) or electrical stimulation of the striatum (Zimmerberg and Glick 1974) cause contralateral turning of the head and body with little circling. Bilateral 6-OHDA-induced lesions of the NAS result in apomorphine-induced locomotor hyperactivity, while bilateral lesions of the striatum

do not (see sections III and IV).

2. Experimental design

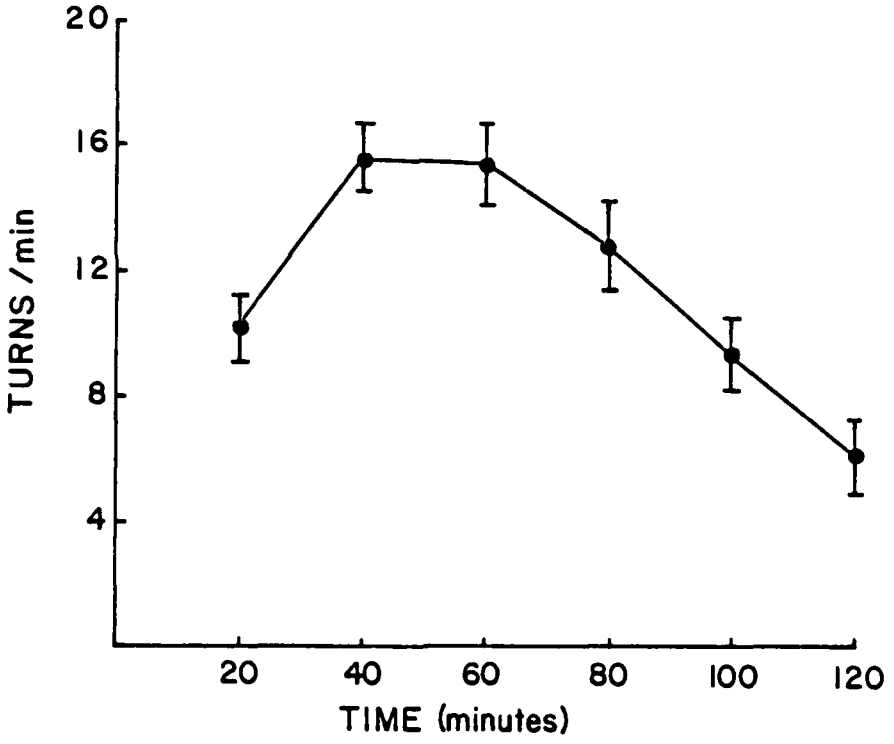
Animals with 6-OHDA-induced lesions were screened by amphetamine-induced rotation 9 days following lesion. Animals thus chosen were then used (at two weeks post 6-OHDA) for intraaccumbens experiments which followed a cross-over design with each animal receiving both vehicle and drug.

3. Results

Direct infusions of dopaminergic agonists into "supersensitive" striatum

Unilateral infusion of SKF 38393 (up to 60 ug), apomorphine (up to 20 ug) and LY 151777 (up to 16 ug) into a dopamine-depleted striatum caused contralateral head turning and body posturing. Circling was not observed. Dopamine depletion in these animals ranged from 40% to 87% (3.50 $\pm$ 0.35 ug/g intact striatum, 0.95 $\pm$ 0.18 ug/g depleted striatum, mean $\pm$ S.E.M., n=6). Systemic injections of amphetamine in these same animals caused expected ipsiversive circling (figure 16), while apomorphine-induced circling was in the contraversive direction, with a peak rate of approximately 4 revolutions/min. at 30 min. post injection

Figure 16. Amphetamine-induced (5 mg/kg) rotation towards the lesion side in animals used for intrastriatal infusion of dopaminergic agonists. Systemic apomorphine caused rotation in the opposite direction.


20
16
12
8
4
TURNS / min
20
40
60
80
100
120
TIME (minutes)

(results not shown).

Effects on amphetamine-induced circling of intraaccumbens GABA or muscimol; Injection rate 1ul/min.

Figures 17 and 18 illustrate the effects of GABA and muscimol on the total turns in the 120 minutes following amphetamine injection. Amphetamine-induced circling was clearly reduced by both compounds, muscimol being approximately 10^4 times more potent than GABA. The duration of the effect of GABA was dose-related (Fig.17).

Effect of muscimol or picrotoxin injected into nucleus accumbens on amphetamine-induced circling; Injection rate 0.11 ul/min

Amphetamine-induced circling was significantly reduced when 40 ng or 200 ng of muscimol in 0.5 ul was infused bilaterally into the nucleus accumbens at the rate of 0.11 ul/min (Fig 19). In the 150 minutes following amphetamine injection animals receiving 40 ng of muscimol made a total of 139 $\pm$ 23 turns (mean + S.E.M.) after intra-accumbens muscimol, and 2114 $\pm$ 546 turns (mean + S.E.M.) after intra-accumbens saline ($p<0.01$, t-test). The corresponding values for animals which received 200 ng of muscimol were 54 $\pm$ 44 and 1866 $\pm$ 259 ($p<0.01$, t-test).

In experiments with intra-accumbens picrotoxin the dose of

Figure 17. Circling towards the side of the 6-OHDA lesion induced by amphetamine (5 mg/kg) after intraaccumbens saline (1 ul) or GABA (125 ug/ 1 ul and 500 ug/ 1 ul). Mean $\pm$ S.E.M. of 6 rats (left panel) and 5 rats (right panel). Animals received GABA or saline in a cross-over design.

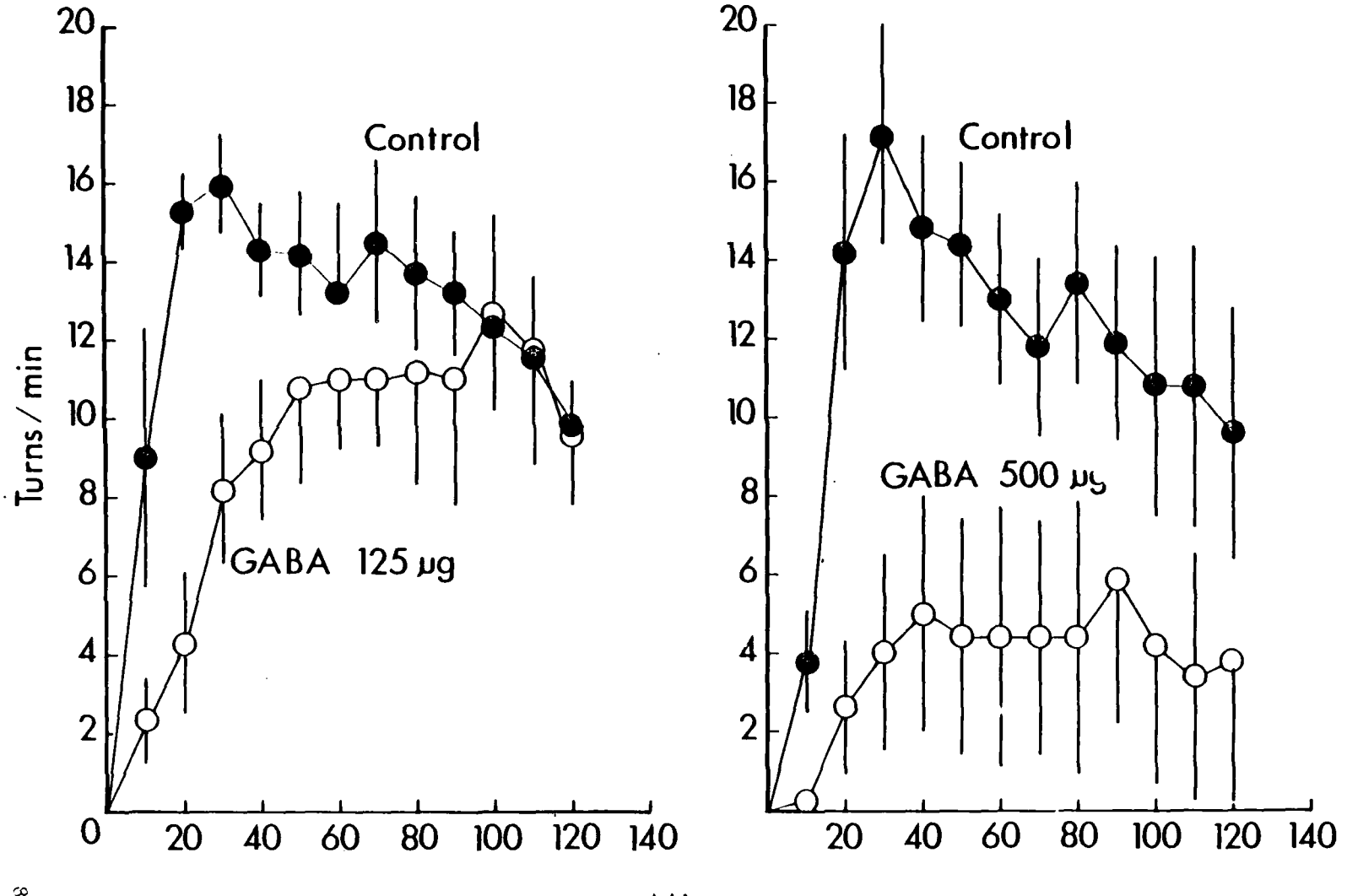

Control
GABA 125 µg
GABA 500 µg
Turns / min
Minutes
0
2
4
6
8
10
12
14
16
18
20
40
60
80
100
120
140

Figure 18. Circling towards the side of the 6-OHDA lesion induced by amphetamine (5 mg/kg) after intraaccumbens saline (1 ul) or muscimol (40 ng/ 1 ul and 200 ng/ 1 ul). Mean $\pm$ S.E.M. of separate groups of 4 rats for each treatment. Animals received muscimol or saline in a cross-over design.

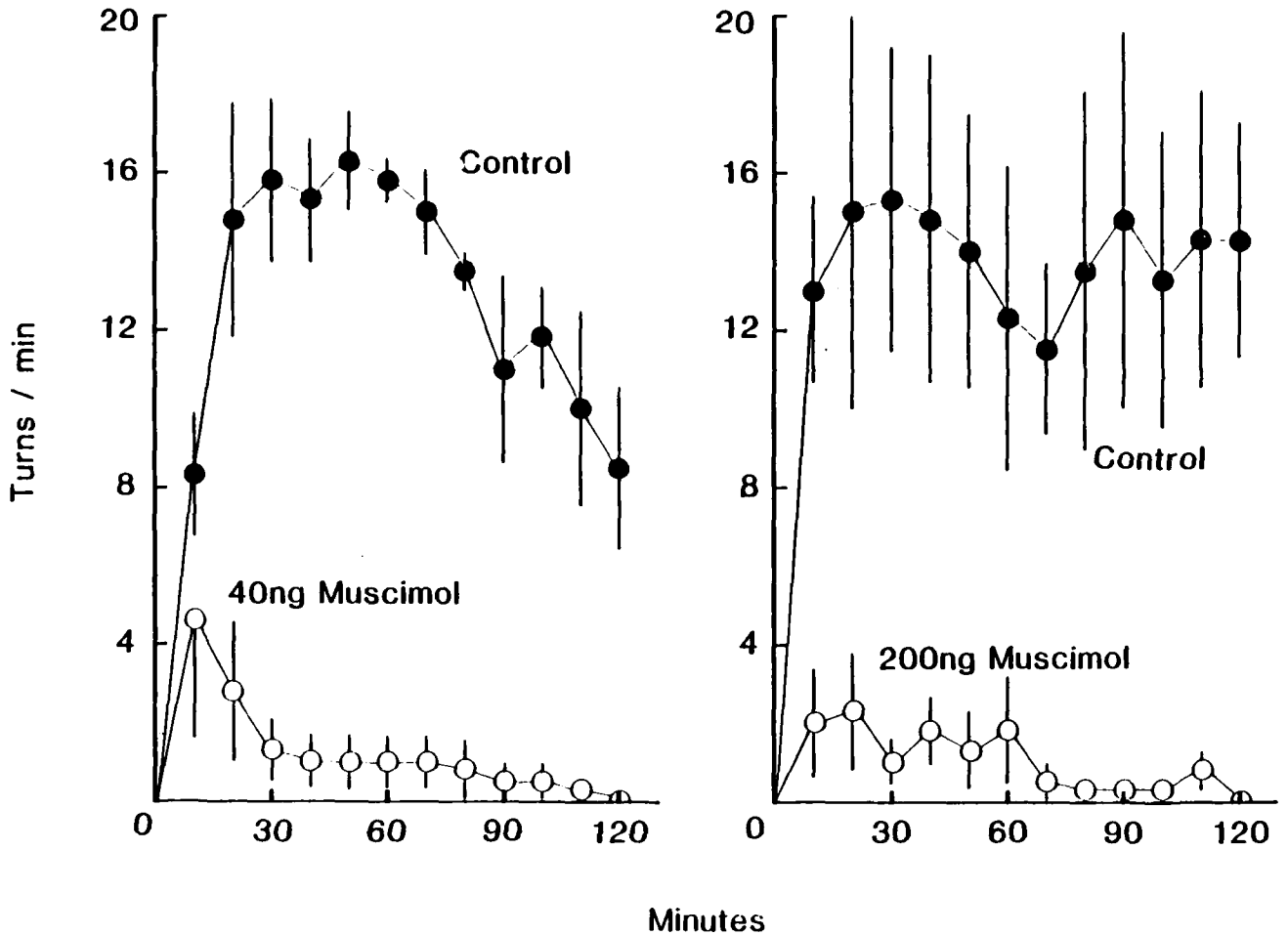
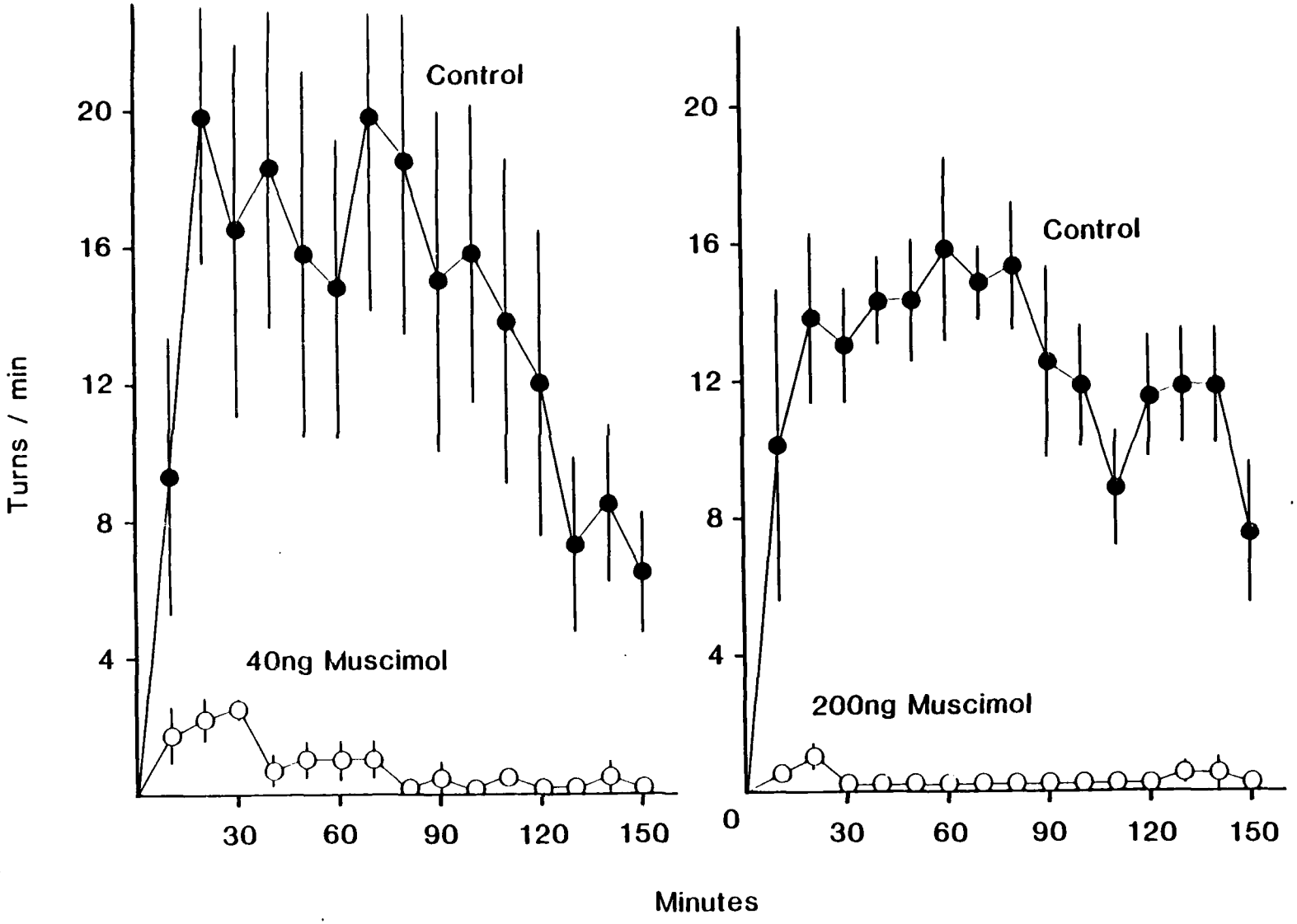
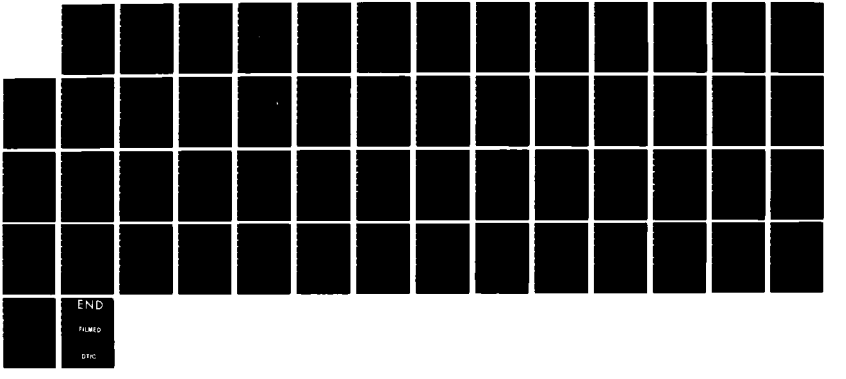
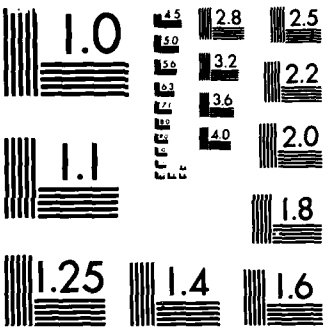

20
16
12
8
4
0
30
60
90
120
Turns / min
Control
40ng Muscimol
Control
200ng Muscimol
Minutes

Figure 19. Amphetamine-induced (5 mg/kg) circling after intraaccumbens saline (0.5 ul) or muscimol (40ng or 200 ng in 0.5 ul). Mean $\pm$ S.E.M. The effect of each dose was assessed in cross-over experiments on separate groups of 4 rats.


Control
40ng Muscimol
Control
200ng Muscimol
Turns / min
Minutes
20
16
12
8
4
0
30
60
90
120
150

AD-A160 821 MESOLIMBIC AND NIGROSTRIATAL DOPAMINERGIC SYSTEMS: 2/2
BEHAVIORAL NEUROPHARMACOLOGY(U) AIR FORCE INST OF TECH
WRIGHT-PATTERSON AFB OH S L HARTGRAVES AUG 85
UNCLASSIFIED AFIT/CI/NR-85-134D F/G 6/15 NL





MICROCOPY RESOLUTION TEST CHART
NATIONAL BUREAU OF STANDARDS-1963-A

amphetamine was reduced to 2.0 mg/kg to allow a facilitatory effect of picrotoxin, if present, to be observed. However, no such effect could be detected after intracranial doses of either 12.5, 50 or 625 ng of picrotoxin, although there was a tendency for the highest dose to increase the initial rate of circling (Fig 20).

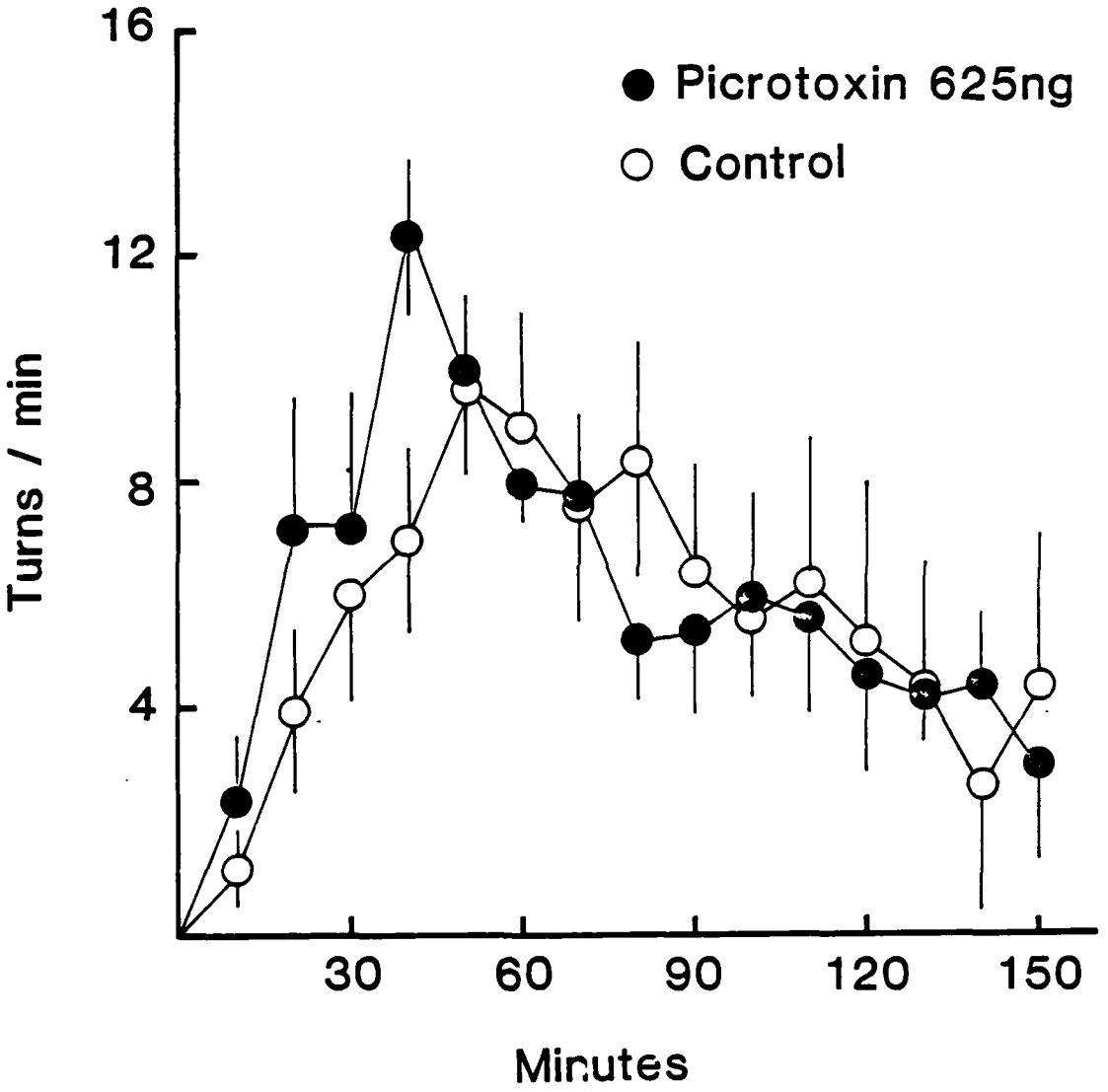
Effect of intra-accumbens muscimol on apomorphine-induced circling in rats with unilateral nigrostriatal destruction and bilateral lesions of mesolimbic dopamine neurons

Muscimol (40 ng, 0.5ul, 0.11 ul/min) significantly reduced the contralateral circling evoked by apomorphine (1 mg/kg SC) in rats with bilateral 6-OHDA-induced lesion of mesolimbic dopamine neurons in addition to their unilateral 6-OHDA-induced nigrostriatal lesion. In the hour after apomorphine injection total turns per rat were 336 $\pm$ 62 after intra-accumbens saline and 119 $\pm$ 83 after intra-accumbens muscimol. These values differed significantly ($p<0.01$, paired t-test, n=5).

4. Discussion

Previous studies have provided evidence that the drug-induced circling of rats with unilateral nigrostriatal lesions depends not only on nigrostriatal dopaminergic activity, but also on

Figure 20. Amphetamine-induced (2 mg/kg) circling after intraaccumbens saline (0.5 ul) or picrotoxin (625 ng). Mean ± S.E.M. of 5 rats. Animals received picrotoxin or saline in a cross-over design.


16
12
8
4
Turns / min
Picrotoxin 625ng
Control
30
60
90
120
150
Minutes

mesolimbic dopaminergic activity in the nucleus accumbens. In rats with unilateral 6-OHDA-induced lesions of the nigrostriatal pathway amphetamine-induced circling was blocked by mesolimbic dopamine neuron destruction (Kelly and Moore 1976; Kelly and Moore 1977; Pycock and Marsden 1978), whereas apomorphine-induced circling was enhanced (Kelly and Moore 1976; Kelly and Moore 1977). Microinjection of haloperidol into the nucleus accumbens reduced the circling provoked by either amphetamine or apomorphine (Kelly and Moore 1977). These results support the view that dopaminergic activity in the nucleus accumbens is able to modulate one of the steps involved in the translation of nigrostriatal dopaminergic asymmetry into circling behavior. In support of the importance of the NAS in drug-induced circling, direct unilateral infusions of dopaminergic agonists (a D-1 specific, a D-2 specific and a mixed agonist) into prior dopamine-depleted striata did not result in circling behavior.

At least two hypotheses may account for the lack of circling noted after intrastriatal infusion, the degree of dopamine depletion and the infusion site. In one study, animals with partial lesions of the nigrostriatal dopamine pathway, resulting in less than 90% destruction of dopaminergic neurons, exhibited no rotation to 1 mg/kg apomorphine (Hefti et al. 1980). These same animals rotated to amphetamine (5 mg/kg), some with only 50% neuronal destruction. In my study, both amphetamine (5 mg/kg) and apomorphine (1 mg/kg) resulted in circling behavior even though

depletion of striatal dopamine was less than 90%. Therefore the lack of rotation following intrastriatal infusion cannot be due to a lack of responsiveness to systemically injected dopaminergic agents. Other investigators have reported predominantly postural deviation with little circling after infusion of dopamine or its agonists into intact striatum (Ungerstedt et al. 1969; McKenzie et al. 1972; Costall et al. 1976), however circling was noted in denervated striatum (Costall et al. 1976). In contrast, following monoamine oxidase inhibition, intrastriatal infusion of dopamine in intact and denervated striatum did result in circling behavior (Ungerstedt et al. 1978; Setler et al. 1978), with the shift to the left in dose-response reported to be from 30 to 100 fold.

The anatomical site of infusion may play a role in circling behavior seen after direct intrastriatal treatment. In this study, my infusion site was in the central part of the striatum which may be less sensitive to agonist-induced circling behavior. Dopamine was reported to be more effective in causing rotation after medial striatal infusion than after lateral striatal infusion, which caused more postural deviation than circling (Joyce and Van Hartesveldt 1984). This may account for some of the aforementioned variable results.

In the experiments concerning alterations of drug-induced circling by intraaccumbens infusions, the results of GABA-ergic activity in the NAS indicates an opposite effect compared to dopamine. Whereas dopamine in the nucleus accumbens facilitates

drug-induced circling, GABA-ergic activity appears to inhibit it, since microinjections of GABA or muscimol into the nucleus accumbens reduced amphetamine-induced circling. These initial results were obtained with injections in a volume of 1 ul at the rate of 1 ul/min. Injection rates and volumes equal to or greater than these are not uncommon in studies of the actions of neurotransmitters in the nucleus accumbens and other brain regions (see Table 2).

Using a slower infusion rate (0.5 ul at a rate of 0.11 ul/min), muscimol was still able to block amphetamine-induced circling. Moreover, similar injections reduced the apomorphine-induced circling of rats with unilateral nigrostriatal lesions and bilateral mesolimbic dopamine neuron destruction. The effect of muscimol on drug-induced circling, therefore, appears to be mediated at least partly on neurons which are postsynaptic to dopaminergic terminals, although a possible additional effect on dopamine release is not excluded. Picrotoxin exerted no effect on amphetamine-induced circling in the doses used here. Since the highest dose elicited signs of seizure activity in two of five animals tested, higher doses were not used. A possible explanation of the lack of effect of picrotoxin is that the GABA-ergic neurons in the nucleus accumbens which inhibit drug-induced circling are near-maximally inhibited by the dose of amphetamine administered. Though conclusive evidence on this point is not available, the observation that GABA turnover in

nucleus accumbens is stimulated by dopamine antagonists (Marco et al. 1976) is consistent with it. Other indirect support for this view is the finding that the predominant response of neuronal cell bodies in the nucleus accumbens to systemically-administered amphetamine is a prolonged depression of firing rate (Bashore et al. 1978; Rebec et al. 1979). It may also be pertinent that in other brain regions the behavioral effect of picrotoxin is not invariably the opposite of that of GABA or muscimol. For example, in a detailed analysis of the behavioral effects of muscimol or picrotoxin injected unilaterally into various nigral loci Kozlowski and Marshall (1980) observed contralateral circling when either agent was injected into the substantia nigra pars reticulata. Others (Olpe et al. 1977) have observed a similar pattern of results when the picrotoxin injection volume was small (0.5 ul) but not when it was larger (2.0ul).

The studies presented here provide evidence that GABA-ergic mechanisms within the nucleus accumbens inhibit the rate of drug-induced circling. This effect appears to be mediated at least partly by an action post-synaptic to the dopaminergic input.

C. Experiment 2: circling-striatonigral lesions

1. Introduction

Another model of circling behavior involves lesions of the descending striatonigral pathway. The perceived role of this pathway in motor activity has changed from one of modulation of dopaminergic neuronal activity (Bunney and Aghajanian 1976; James and Starr 1978; Dray 1979) to a major function as an output system via substantia nigra pars reticulata non-dopaminergic neurons (Garcia-Munoz et al. 1977; Marshall and Ungerstedt 1977a; DiChiara et al. 1978). Circling behavior is thought to result from GABA-mediated inhibition of these pars reticulata neurons (DiChiara et al. 1979b; Olianas et al. 1978).

An elegant method used to quantitatively determine the effects of supersensitization of the striatum on circling behavior uses lesions of the striatonigral pathway (Marshall and Ungerstedt 1977b; Mandel and Randall 1985). In this paradigm, baseline circling rates to apomorphine are determined following electrolytic lesion of one striatonigral pathway. Dose-responses to apomorphine following additional 6-OHDA-induced lesions destroying the dopamine input to the contralateral striatum (the side that was driving the baseline circling rate), are then employed to derive estimates of supersensitization. These

estimates have ranged from 10-40 fold increases in sensitivity to apomorphine. A problem concerning these studies is the inclusion of 6-OHDA-induced damage to the nucleus accumbens, a structure known to influence circling behavior. Techniques designed to limit damage to mesolimbic nuclei while still depleting striatal dopamine (Jackson et al. 1983) would give a clearer picture of the effects of striatal supersensitization.

Two questions will be addressed by these studies: Why are shifts in this striatally derived behavior 10-40 fold when that predicted by a 30% up regulation of dopamine receptors and observed in stereotypic behavior (Randall and Randall, in prep) only 2 fold?; What is the contribution of dopamine depletion in the nucleus accumbens to the large shift in the striatonigral model of circling?

2. Experimental design

Dose response curves for apomorphine-induced rotational behavior in the striatonigral model used 9 doses at equal log-intervals. Only animals which rotated to both apomorphine and amphetamine screening sessions were used in the study. Animals (n=24) received 4 of the 9 doses pre 6-OHDA and every dose (except the highest dose) post 6-OHDA. Each test day was separated by 1 week. Where possible ED_{50}'s were calculated using weighted least squares estimation of the four parameters using ALLFIT (De Lean et al.

1978). Minimum response was constrained to zero and where necessary maximum response constrained to the maximum response observed.

3. Results

Effects of contralateral striatal 6-OHDA

6-OHDA-induced lesions of the opposite striatum resulted in a 2-4 fold shift to the left of the dose-response curve (Figure 21). This group of rats had a depletion of 75% in the 6-OHDA-lesioned striatum and a 23% up regulation of dopamine recepors (Table VI).

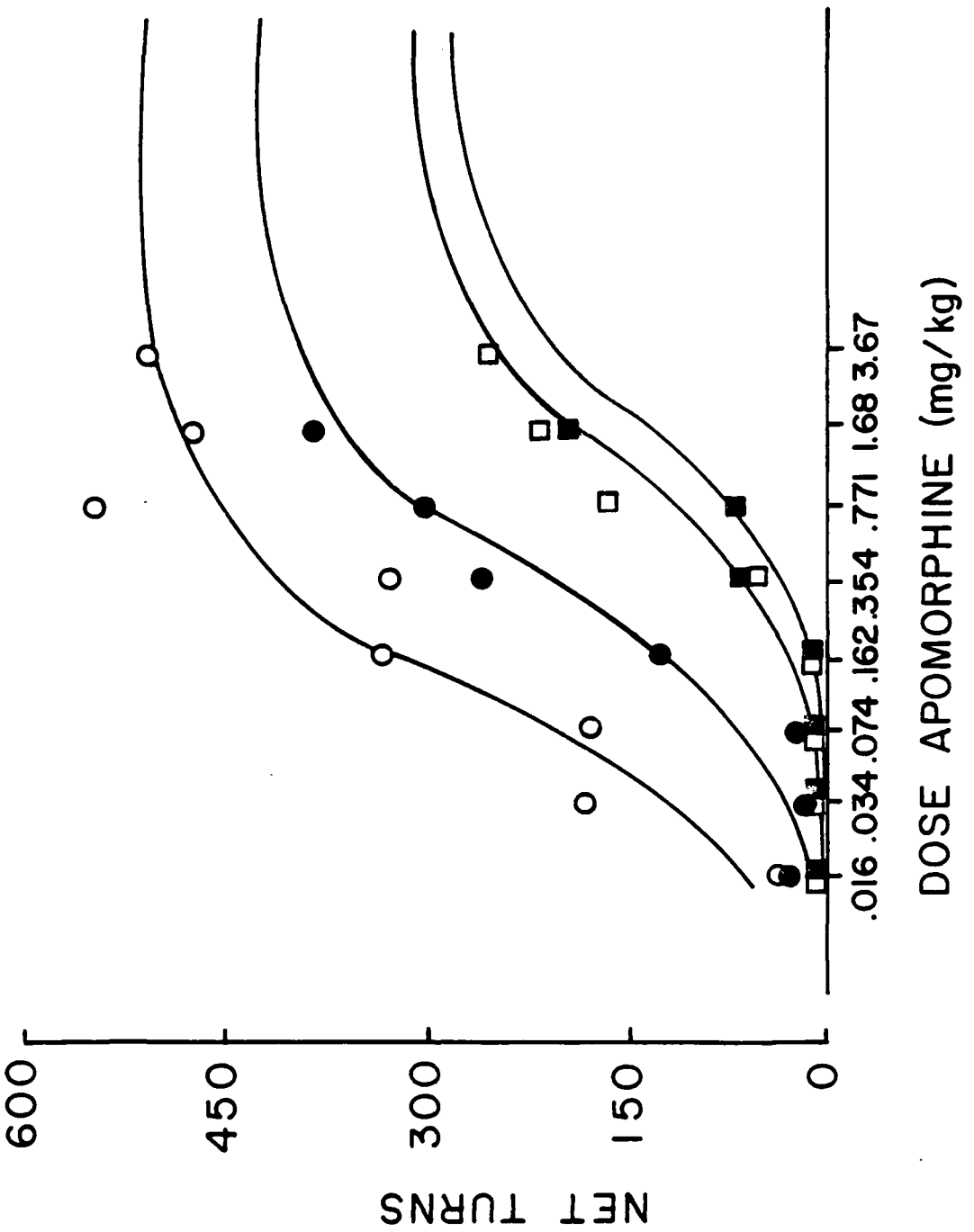
Effects of contralateral medial forebrain bundle (MFB) 6-OHDA

Lesions of the opposite MFB with 6-OHDA resulted in a 12-20 fold shift to the left of the dose-response curve (Figure 21). Striatal dopamine depletions were 61% with an increase of ^{3}H-spiperone binding of 24% (Table VI).

Effects of bilateral lesions of the nucleus accumbens with 6-OHDA

Bilateral lesions of the nucleus accumbens with 6-OHDA caused depletions of 71% in the NAS, while depleting striatal dopamine by 25% (Table VI). There was no increase in striatal ^{3}H-spiperone

Figure 21(A,B). Dose-response curves for apomorphine-induced rotation in animals with striatonigral electrolytic lesions alone (open squares), or with additional 6-OHDA-induced lesions of the opposite striatum (shaded circles), the medial forebrain bundle (MFB, open circles) or the nucleus accumbens (NAS, shaded squares). Curves in Figure 21A were calculated with each curve having its own maximum, while in 21B maximum responses were shared for all curves. 6-OHDA-induced lesions of the opposite striatum caused a 2-4 fold shift to the left in apomorphine sensitivity while lesions of the opposite MFB caused a 12-22 fold shift. Rotation of animals with bilateral lesions of the NAS was not significantly different from output lesioned animals alone. There was an overall effect of treatment ($F(7,126) = 8.33$; $p < 0.01$) and an overall group effect ($F(2,18) = 15.2$; $p < 0.01$). Differences between groups were also significant: MFB vs striatum ($F(1,18) = 8.07$; $p < 0.05$), MFB vs NAS ($F(1,18) = 30.39$; $p < 0.01$) and striatum vs NAS ($F(1,18) = 7.14$; $p < 0.05$). The slope of the curve in A is 3.58, with the MFB group representing a shift of 12.65 fold compared to output lesion alone. The slope in B is 3.74 with the MFB group representing a shift of 22.37 fold.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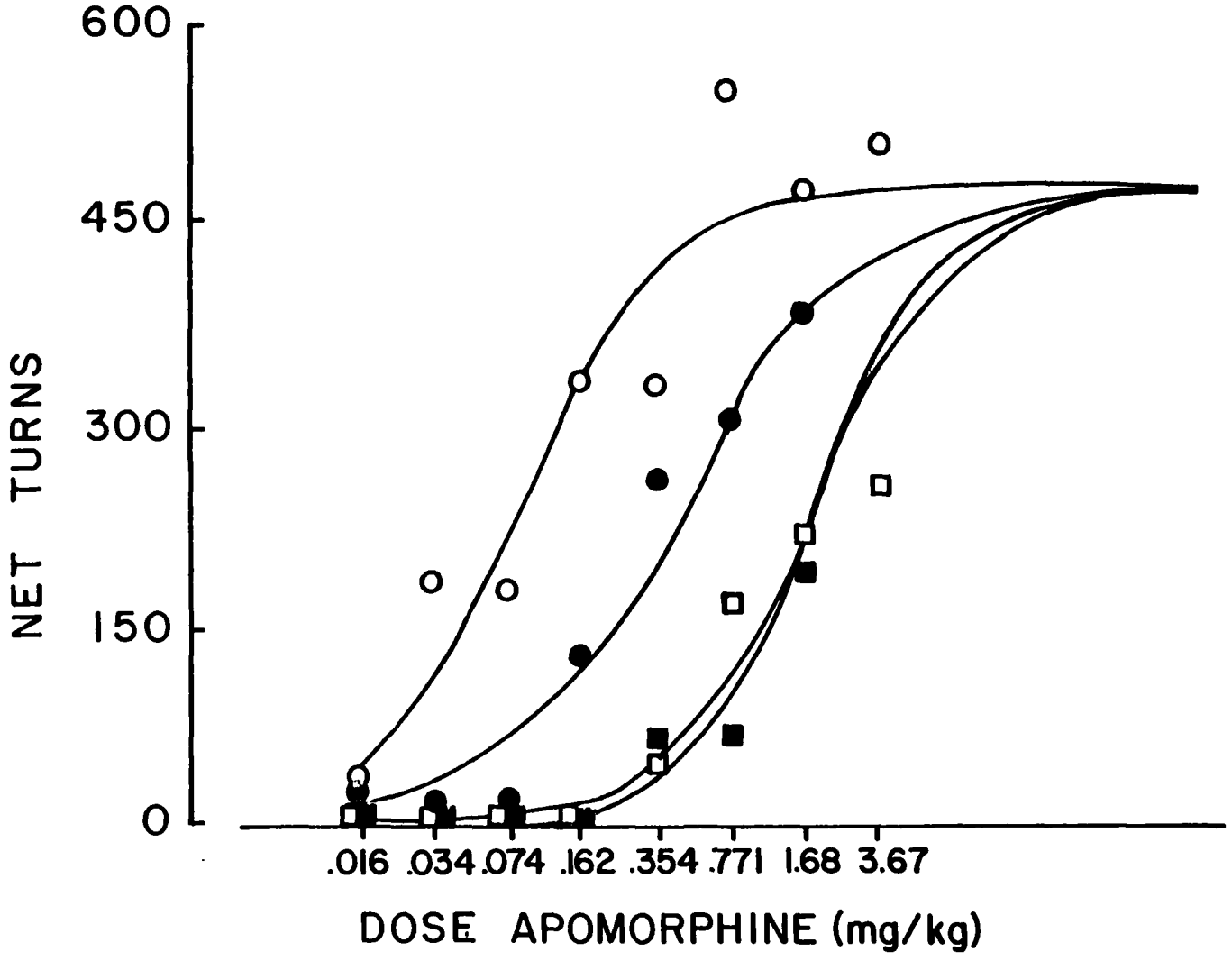
0
.016 .034 .074 .162 .354 .771 1.68 3.67
DOSE APOMORPHINE (mg/kg)


600
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NET TURNS
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DOSE APOMORPHINE (mg/kg)

Table VI
Biochemical data

Group	n	Dopamine (ng/mg)	Binding (fmoles/mg)	Kd
Control	6			
STR (pooled)		10.76 ± 0.46	437 ± 30	167 ± 18
NAS (pooled)		7.80 ± 0.26	---	---
MFB	7			
STR (L)		4.23 ± 1.46*	577 ± 28*	149 ± 19
STR (R)		10.71 ± 0.54	415 ± 13	160 ± 17
NAS (L)	4	2.52 ± 1.20*	---	---
STR	7			
STR (L)		2.69 ± 0.60*	567 ± 34*	191 ± 13
STR (R)		9.68 ± 0.56	403 ± 17	156 ± 21
NAS (L)	3	7.14 ± 0.55	---	---
NAS	6			
STR (L)		7.06 ± 0.49*	391 ± 25	152 ± 10
STR (R)		8.97 ± 0.69	401 ± 24	167 ± 17
NAS (pooled)		2.28 ± 0.24	---	---

Medial forebrain bundle (MFB), Striatum (STR), Nucleus accumbens (NAS) pooled: left (L) + right (R) * $p < 0.01$, pooled t-test

binding, however, the loss of dopamine in the left striatum was significantly different than control. This could be due to dissection variation or a compensatory decrease in dopaminergic function secondary to the striatonigral lesion on the opposite side (Costall et al. 1983). Lesions of the nucleus accumbens did not enhance rotational behavior, but actually tended to diminish it (Figure 21).

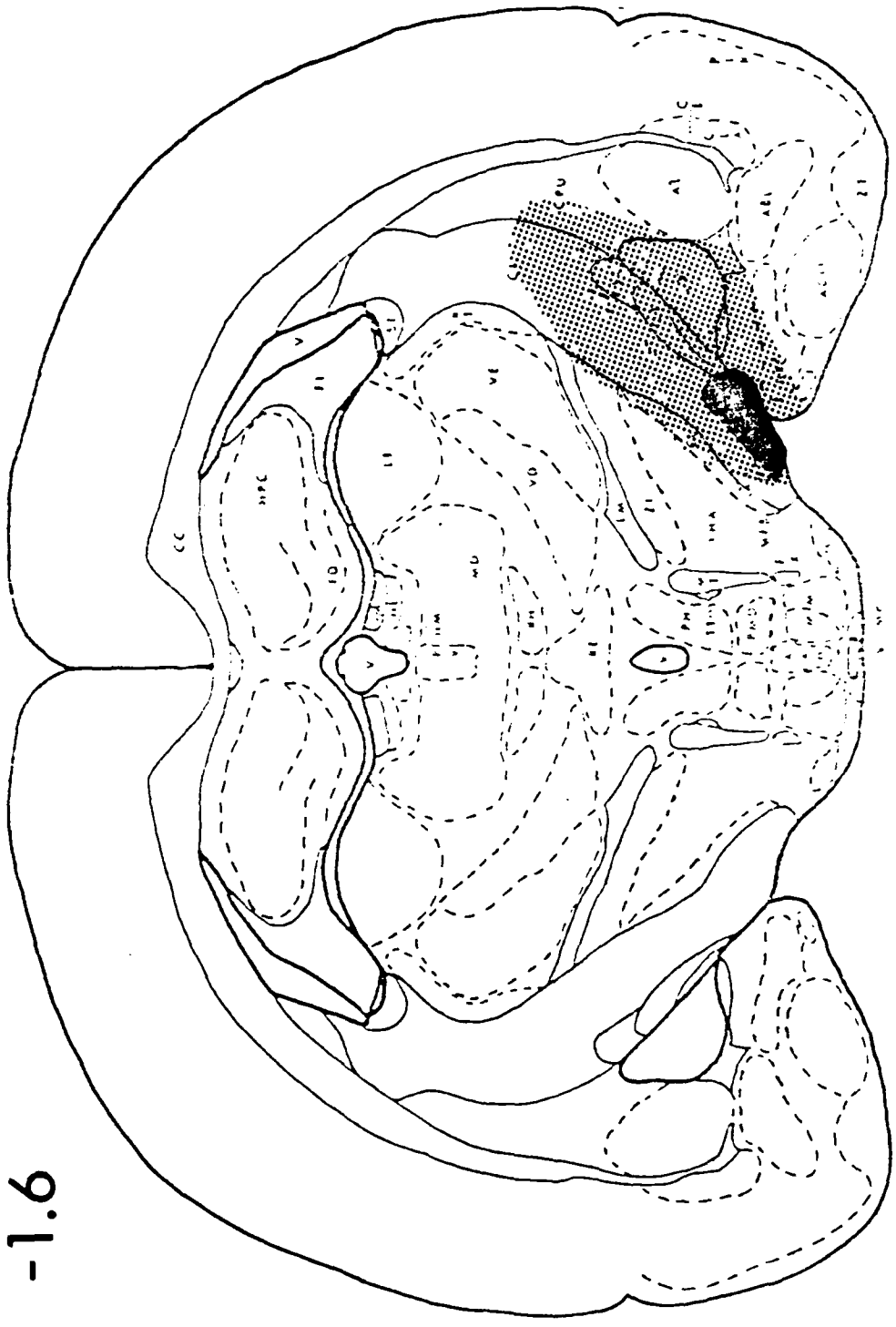
Histological verification of electrolytic lesion site

Figure 22 depicts the area involved in lesions of the striatonigral pathway. No damage could be seen in the entopeduncular nucleus of rats used in this study, and the minimal amount of dopamine depletion on the side of the electrolytic lesions argues against damage to the medial forebrain bundle.

4. Discussion

The use of the striatonigral "output" circling model to assess 6-OHDA-induced supersensitization has typically yielded estimates of up to 40 fold increases in sensitivity to apomorphine. These estimates have not taken into account the contribution of the nucleus accumbens, which is known to enhance apomorphine-induced circling in rats with unilateral striatal dopamine depletion (Kelly and Moore 1976). Here we show that rats

Figure 22. Effects of electrolytic lesion of the striatonigral "output" pathway. Effective lesions always included parts of the ventral internal capsule. No damage could be seen in the entopeduncular nucleus of rats with effective lesions.



-1.6

with lesions specific to the striatum (typically causing only 10-15% NAS depletion) which do cause supersensitization (increased striatal ^{3}H-spiperone binding of approximately 25%) do not exhibit the large shifts to the left in apomorphine sensitivity. In fact the 2-4 fold shift observed in these animals is much more in line with the 2 fold shift to the left in sensitivity to apomorphine-induced stereotypy noted in mice treated chronically with neuroleptics (causing approximately 30% increased binding, Randall and Randall, in prep). In the group of animals with lesions in the medial forebrain bundle, meant to deplete dopamine in both striatum and NAS, shifts to the left in sensitivity to apomorphine were in the range of 12-20 fold, even though striatal binding in this group was essentially the same as in the striatal alone group. These results help explain the variable estimates of the impact of supersensitization on shifts in the dose-response curve for drug-induced circling, and additionally confirms the importance of the nucleus accumbens in circling following unilateral 6-OHDA-induced lesions of the nigrostriatal pathway.

Best fitting curves (weighted, least squares, 3 parameter logistic function) for the dose-response to apomorphine in the output model are shown in Figure 21A and 21B with independent or shared maximum responses, respectively. Although visually the alteration in maximum response appears obvious in Figure 21A, the difference between the two fits was not significant ($F < 1$) suggesting that the slopes of the curves at lower doses are

consistent with equivalent maximum response. Review of video tapes suggest that competing behaviors were probably responsible for the blunted maximum responses at higher doses. Thus, as in the case of locomotor activity where at higher doses of apomorphine stereotypic behavior interferred with locomotion, rotation at higher doses was also interferred with by stereotypic grooming, or other high dose response characteristics. Supersensitive MFB animals rotated at much lower doses of apomorphine than supersenstive striatal animals. At these lower doses the competing behavior (in this case stereotypic grooming of the contralateral body surface) was less likely to be expressed in the MFB group, creating an apparent increase in maximum response.

Another interesting result concerns the influence of the nucleus accumbens alone on apomorphine-induced circling behavior in the output model. It was anticipated that the role of the NAS would be similar to its role after nigrostriatal lesion, especially since the NAS is known to contribute fibers to the substantia nigra (Swanson and Cowan 1975; Conrad and Pfaff 1976; Nauta et al. 1978), and dopamine infused into the substantia nigra pars reticulata stimulates locomotor activity (Jackson and Kelly 1983). Instead, supersensitization of NAS not only failed to enhance circling, it actually shifted the dose-response curve to apomorphine slightly to the right. Therefore, this suggests that the interaction of NAS dopaminergic activity with that in striatum occurs via efferents other than those lesioned in this study, and

that NAS activation may actually interfere with circling after striatonigral lesions.

Two possible sites where the nucleus accumbens and the striatum could interact to produce circling are the globus pallidus (GP) and the thalamus. The globus pallidus receives afferents from both the nucleus accumbens and the striatum (Wilson 1914; Fox et al. 1974; Swanson and Cowan 1975; Conrad and Pfaff 1976; Pycock and Horton 1978), and pharmacological manipulation of the GP influences circling and locomotor activity (Jones and Mogenson 1980; Costall et al. 1972; Dewar et al. 1983). In a recent study, it was found that different opiate receptor agonists preferentially stimulated either locomotion (bilateral infusion) or circling (unilateral infusion) from the same pallidal region (Dewar et al. 1985). The fact that a major enkephalin pathway from the striatum is known to innervate the GP (Cuello and Paxinos 1978; Bayon et al. 1981) coupled with evidence that opiate receptors can modify locomotion and circling further suggests the GP as an important site integrating the necessary components for circling behavior. Anatomically, the globus pallidus sends collateral projections to both the striatum and the substantia nigra pars reticulata, suggesting that this structure may have a greater role in overall regulation of the basal ganglia than previously thought (Staines and Fibiger 1984). In addition, the GP is associated with other motor structures such as the ventral thalamic nuclei, substantia nigra and pedunculopontine nucleus

(Parent and De Bellefeuille 1983).

The ventral tier nuclei of the thalamus is another region where the nucleus accumbens and striatum may interact. Muscimol infused into the ventromedial nucleus of the thalamus depressed muscimol-induced contralateral circling from the ipsilateral SNR (Starr and Summerhayes 1983). These infusions were interpreted as having more effect on locomotion than posturing. As well, electrolytic lesions of the ventromedial nucleus ipsilateral to a nigrostriatal 6-OHDA-induced lesion inhibited circling (Garcia-Munoz et al. 1983). Although there is only nominal pharmacological evidence for locomotion associated with the thalamus, there is a report of a pathway from the subpallidal region to the mediodorsal thalamus which may contribute to locomotor activity (Heimer et al. 1982). The close proximity of terminal projections from the entopeduncular nucleus and SNR to the thalamus further implies an important role for the thalamus in processing motor behaviors.

Another issue raised by these studies is the contention that both behavioral and receptor supersensitivity require 80-90% dopamine depletion (Creese and Snyder 1979; Hefti et al. 1980; Neve et al. 1982). In the present study lesions resulting in depletions of 61% and 75% caused both behavioral (up to 20 fold shift in sensitivity to apomorphine) and biochemical (24% increase in ^{3}H-spiperone binding) supersensitivity. Thus, the regions of the forebrain dopamine system that become supersensitive (striatal

only or varying combinations of damage to both striatum and NAS) may variably influence behavioral measures, as evidenced by the dose response shifts in the present study.

In summary, the nucleus accumbens appears to be the structure responsible for the variable estimates of behavioral supersensitivity in the striatal output circling model. Those who choose to use this model in the future should detail the effects of dopamine depletion in this nucleus when reporting results.

D. Experiment 3: locomotor hyperactivity

1. Introduction

Locomotor hyperactivity involving the nucleus accumbens has been introduced in section III. In a study completed 10 yrs ago, it was noted that bilateral 6-OHDA-induced lesions of the striatum (sparing NAS dopamine fibers) reduced amphetamine-induced (5.0 mg/kg) stereotypic behavior while enhancing locomotor activity (Kelly et al. 1975). This dose of amphetamine causes intense stereotypy (and little locomotor activity) in intact animals, suggesting a masking of locomotion by stereotypic behavior. It is also of interest that intraaccumbens muscimol potentiates the stereotypic effects of low doses of systemic apomorphine (Scheel-Kruger et al. 1977b), basically suggesting that each behavior can compete with the other. In this section the apparent

masking effect of striatal originated behaviors on locomotor hyperactivity will be examined by comparing the effects of direct NAS infusions of apomorphine to systemic injections.

2. Results

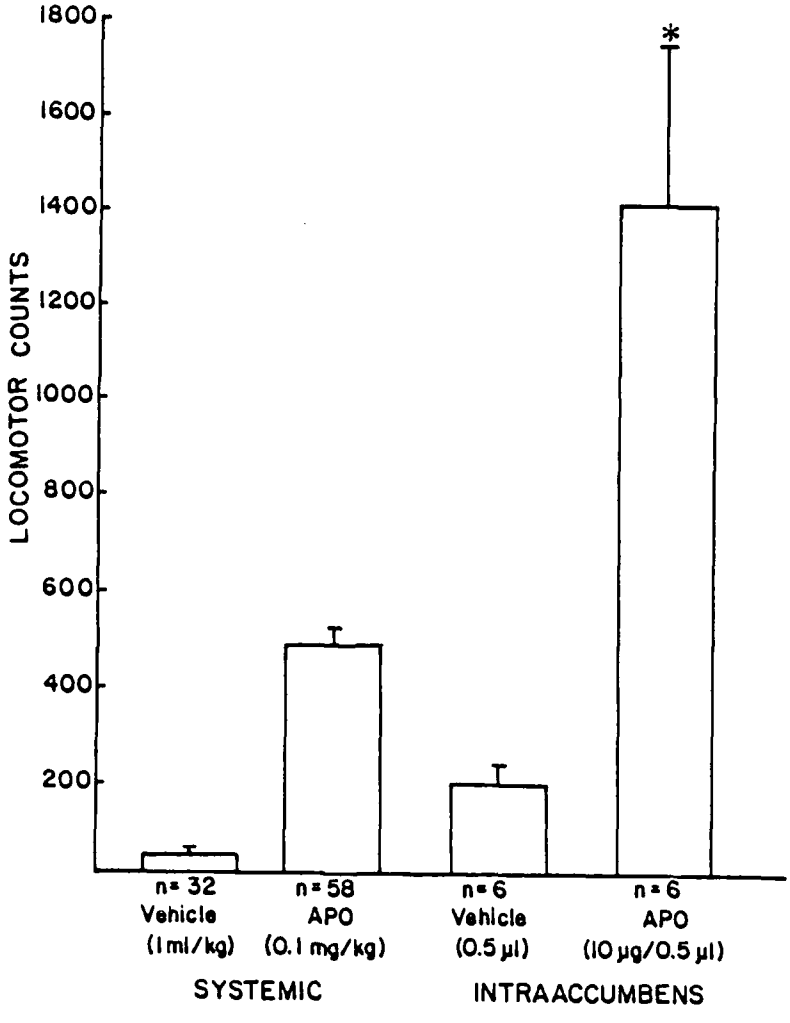
Intraaccumbens versus systemic apomorphine

The infusion of 10 ug of apomorphine bilaterally into dopamine-depleted NAS caused 1416 $\pm$ 334 (mean $\pm$ S.E.M., n=6) locomotor counts in the 60 minutes following infusion. As seen in Figure 23, compared to systemic injections, this represents almost 1000 counts more than injections of 0.1 mg/kg apomorphine in animals with bilateral 6-OHDA-induced lesions of the NAS (487 $\pm$ 33, n=58, $p<0.005$, pooled t-test, 2 tailed). It was found in section III that 0.1 mg/kg apomorphine was the most effective dose tested in producing locomotion in rats with bilateral lesions. Higher doses (0.2 mg/kg, 0.25 mg/kg) tended to diminish the locomotor response. The large "n" for the systemic group is due to the use of this dose for initial screening of groups used in section III.

3. Discussion

The effects of high doses of systemic dopaminergic agents in

Figure 23. Comparison of locomotor effects caused by intraaccumbens apomorphine (10 ug) in supersensitive NAS versus systemic apomorphine (0.1 mg/kg) in animals with supersensitive NAS. Intraaccumbens apomorphine differed significantly from systemic apomorphine ($p < 0.005$; pooled, 2-tailed t-test).


1800
1600
1400
1200
1000
800
600
400
200
LOCOMOTOR COUNTS
*
n = 32
Vehicle
(1 ml/kg)
n = 58
APO
(0.1 mg/kg)
n = 6
Vehicle
(0.5 µl)
n = 6
APO
(10 µg/0.5 µl)
SYSTEMIC
INTRAACCUMBENS

rats can be interpreted in at least two ways. Locomotor activity (as well as investigatory behavior) and focused stereotypic behavior may represent progressively greater stimulation along a single continuum, or the effects of drugs are due to activation at different anatomical sites or perhaps different biochemical receptor sites. The latter suggests a concept termed parallel processing (Lyon and Robbins 1975) where drug-induced behavioral competition arises from different anatomical regions, e.g. locomotion from the nucleus accumbens and gnawing/licking from the striatum. The behavior that predominates in the parallel model would depend upon which anatomical site was preferentially stimulated by a set dose of drug. Thus, low doses of amphetamine or apomorphine would preferentially stimulate the NAS while high doses would stimulate the striatum (Robbins and Everitt 1982).

In support of the parallel processing hypothesis, I report here that direct infusion of apomorphine into supersensitive NAS results in much higher locomotor activity compared to systemic injection (although attempts were not made to test doses of apomorphine higher than 0.25 mg/kg, since observation of the animals revealed stereotypic behavior). In addition, the dose-response curve for apomorphine-induced locomotor activity in animals with supersensitive NAS indicated a maximal effect around 0.1 mg/kg, with a tendency for a diminished response to 0.2 mg/kg especially in the first 30 minutes (see Figure 2). In section III the masking effect in control animals (especially in the first 30

minutes following injection) of apomorphine-induced stereotypic behavior on locomotor activity is apparent in Figure 1. Others have noted behavioral changes including hyperactivity in cats (Villablanca et al. 1976) and monkeys (Denny-Brown and Yanagawa 1976) following extensive, bilateral striatal lesions. Further support for competition between anatomical sites was reported by Morelli et al. 1980) in rats with prior (2 weeks) kainic acid lesions of the substantia nigra pars reticulata. These animals exhibited enhanced sniffing and decreased gnawing to a dose of apomorphine that caused intense gnawing in control animals.

In this study it has been observed that stereotypic behavior competes and eventually masks locomotor activity in three different models. Control animals given apomorphine have only the narrow dose range of $0.1 < X < 0.4$ mg/kg that stimulated locomotion. In animals with supersensitive accumbens, doses of apomorphine greater than 0.1 mg/kg tended to diminish locomotor counts compared to the peak effect caused by 0.1 mg/kg. And finally, direct infusions of apomorphine resulted in much higher locomotor counts compared to systemic injections.

E. Experiment 4: stereotypic grooming

1. Introduction

Dopamine agonist-induced stereotypic grooming is associated

with bilateral dopamine depletion of the striatum (see section IV). As noted in the discussion of section IV, ACTH also induces a form of grooming in rats which is associated with the striatum. Since ACTH-induced grooming may be influenced by nucleus accumbens lesions (Springer et al. 1983; Dunn and Iversen 1984) and intraaccumbens ACTH has been reported to cause grooming (Ryan et al. 1983), the effects of NAS lesions on stereotypic grooming will also be examined. These studies may shed light on the differences between intraventricular administrations of 6-OHDA to adult rats which do not result in stereotypic grooming (Breese et al. 1984) compared to direct lesions of the nigrostriatal pathway which do.

2. Experimental design

In this experiment, apomorphine was systemically injected into rats with dopamine-depleted NAS or infused into intact NAS of rats with prior, bilateral 6-OHDA-induced lesions of the striatum. In rats bearing lesions of both NAS and striatum, striatal lesions and NAS cannulations were done at the same time. After baseline testing for stereotypic grooming, additional 6-OHDA lesions of the NAS were made in awake animals via the indwelling cannulae. These animals were subsequently retested to compare the effects of the NAS on stereotypic grooming.

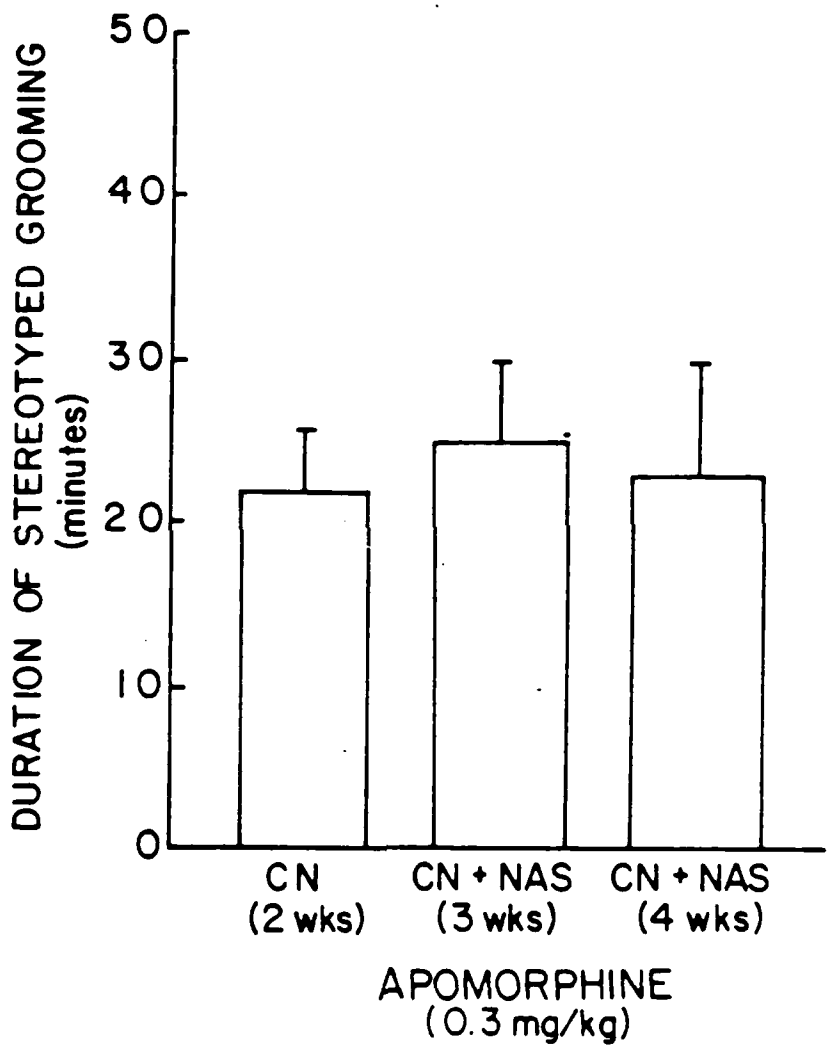
3. Results

Influence of nucleus accumbens on stereotypic grooming

In animals with only 6-OHDA-induced lesions of the nucleus accumbens (NAS), systemic injections of apomorphine never caused stereotypic grooming, but did produce expected hyperactivity (see section III). Likewise, direct, bilateral infusion of apomorphine (10 ug) into supersensitive NAS did not cause stereotypic grooming, but did cause locomotor hyperactivity. Moreover, bilateral 6-OHDA-induced lesions of the NAS given subsequent to bilateral 6-OHDA-induced lesions of the striata did not alter the stereotypic grooming response (Figure 24). 6-OHDA-induced lesions of the NAS (in rats with prior 6-OHDA-induced lesions of the striata) were confirmed by inspection of cannulae tracks into the NAS. Typically these lesions cause an average dopamine depletion of 72% in the NAS, 75% in the olfactory tubercle and 17% in the striatum, n=64.

In rats with bilateral 6-OHDA-induced lesions of the striata, apomorphine (10 ug) infused bilaterally into intact NAS also caused stereotypic grooming (17 $\pm$ 4 minutes, mean $\pm$ S.E.M., n=4). The latency for the appearance of this behavior was similar to caudate infusions. When the same animals were infused with either haloperidol (5 ug) or vehicle into the NAS and then administered

Figure 24. Effects of additional NAS depletion on apomorphine-induced stereotypic grooming (n=11,n=10,n=9, respectively). Non significant differences, $p > 0.05$, Mann-Whitney U test, Mean $\pm$ S.E.M.


DURATION OF STEREOTYPED GROOMING
(minutes)
50
40
30
20
10
0
CN
(2 wks)
CN + NAS
(3 wks)
CN + NAS
(4 wks)
APOMORPHINE
(0.3 mg/kg)

apomorphine (0.075 mg/kg, sc) 30 minutes later. vehicle infused rats engaged in stereotypic grooming for 28 ± 5 minutes (n=4), while haloperidol reduced this time to 15 ± 2 minutes (mean ± S.E.M., n=3).

4. Discussion

Although the caudate nucleus seems to be the primary structure involved in stereotypic grooming (since the lesions were specific to this nucleus and because local infusion of apomorphine into the caudate was as effective as systemic injection), the involvement of the other major dopamine containing structure, the NAS, is equivocal. Infusion of apomorphine into denervated NAS did not cause stereotypic grooming, but in rats with dopamine depleted striata, infusion into intact NAS did. Also, intra-NAS haloperidol decreased systemic apomorphine-induced stereotypic grooming. These results may be due to spread of drug into the surrounding striatum, which does occur, even at our relatively slow infusion rates (see Table 2, methods section).

It is unlikely that the absence of stereotypic grooming noted by Breese et al. 1984 (in animals with bilateral striatal dopamine depletion secondary to ICV 6-OHDA) is due to depletion of NAS dopamine. In this study depletion of striatal dopamine alone or in combination with accumbens depletion resulted in similar duration of stereotypic grooming.

F. General conclusion

In this section the interaction of the nucleus accumbens with the striatum was examined for drug-induced behaviors ranging from circling to stereotypic grooming. It appears that circling was very dependent on cooperative activity between both the NAS and striatum, as this behavior was usually depressed when one of these two structures was not involved. Drug-induced locomotor activity tended to be overwhelmed by stereotypic activity except for direct dopaminergic-agonist infusion into the NAS. This probably is anatomically based, considering the size of each structure and dopamine content. Finally, stereotypic grooming was unaltered by NAS manipulation.

VI. CONCLUSION

This dissertation has examined drug-induced behaviors associated with the nucleus acumbens and striatum. The use of 6-Hydroxydopamine to anatomically enhance a behavior emanating from one of the above structures (by allowing doses of drugs low enough to prevent major behavioral competition from the other) was only partially successful. Thus, locomotor hyperactivity and circling were enhanced by 6-OHDA-induced lesions of the nucleus accumbens and the medial forebrain bundle, respectively. Bilateral lesions of the striatum did not result in simple enhancement of stereotypic behavior, but instead caused an unique, self-directed behavior termed stereotypic grooming.

Competition between the nucleus accumbens and the striatum for behavioral expression was evident in most of these studies. For example, in control animals stereotypic behavior masked locomotor activity except for a very narrow dose range of apomorphine. Likewise, circling behavior in the output model was reduced at the higher doses of apomorphine by stereotypic grooming. Stereotypic grooming itself (in animals with bilateral striatal lesions) was not affected by accumbens lesions.

Circling behavior in the last section emphasized the importance of the nucleus accumbens in both the nigrostriatal and striatonigral models. Circling in the nigrostriatal 6-OHDA model

was reduced by GABA-ergic manipulation of the nucleus acumbens, while lesions of the nucleus accumbens and striatum (MFB group) accounted for the large shifts in apomorphine-induced rotation noted in animals with striatonigral electrolytic lesions.

Hopefully, these studies have shed additional light on the anatomical basis for drug-induced behaviors arising from the forebrain dopamine systems. Through an understanding of the effects of drugs on these systems in lower animals, perhaps therapies for human patients with diseases of these same systems can be improved.

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